Trustees of Dartmouth College
Standard Operating Procedures
Human Research Protection Program (HRPP)

March 2, 2017
Contents

1 Dartmouth Human Research Protection Program ............................................... 9
  1.1 Mission .............................................................................................................. 9
  1.2 Institutional Authority ....................................................................................... 10
  1.3 Definitions ....................................................................................................... 10
  1.4 Ethical Principles ............................................................................................. 13
  1.5 Regulatory Compliance ................................................................................... 14
  1.6 International Conference on Harmonization-Good Clinical Practice (ICH-GCP) 14
  1.7 Federalwide Assurance (FWA) ....................................................................... 14
  1.8 Research Under the Jurisdiction of Dartmouth ............................................... 15
  1.9 Written policies and procedures ...................................................................... 16
  1.10 Dartmouth’s HRPP Structure ....................................................................... 16
  1.11 Institutional Official ........................................................................................ 16
  1.12 IRB Office Director ........................................................................................ 18
  1.13 IRB Staff .......................................................................................................... 19
  1.14 Institutional Review Board (IRB) ................................................................... 19
  1.15 Legal Counsel’s Office .................................................................................... 19
  1.16 Department Chairs and/or Institutional Leaders .............................................. 20
  1.17 The Investigator ............................................................................................. 20
  1.18 Other Related Units ........................................................................................ 20
  1.19 Protocol-Specific Coordination .................................................................... 22
  1.20 Collaborative Research Projects .................................................................. 23

2 Quality Improvement ............................................................................................. 24
  2.1 External Monitoring, Audit, and Inspection Reports ........................................ 24
  2.2 Investigator Compliance Reviews ................................................................... 25
  2.3 IRB Compliance Reviews .............................................................................. 25
  2.4 HRPP Quality Assessment and Improvement ................................................. 26

3 Education ............................................................................................................... 27
  3.1 Ongoing Education of IRB Chairman, Members, and Staff ............................. 27
  3.2 Ongoing Education of Investigators and Research Team ............................... 28
    3.2.1 Initial Education ....................................................................................... 29
    3.2.2 Continuing Education and Recertification .............................................. 29

4 Institutional Review Board .................................................................................... 30
  4.1 IRB Authority ................................................................................................... 30
  4.2 Roles and Responsibilities .............................................................................. 31
    4.2.1 IRB Chair .................................................................................................. 31
    4.2.2 IRB Members ........................................................................................... 32
    4.2.3 Alternate IRB members ............................................................................ 33
    4.2.4 Subcommittees of the IRB ...................................................................... 33
  4.3 IRB Membership .............................................................................................. 33
  4.4 Composition of the IRB ................................................................................... 34
    4.4.1 Appointment of Members to the IRB ....................................................... 35
    4.4.2 IRB Registration Updates ........................................................................ 35
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5</td>
<td>Use of Consultants</td>
<td>35</td>
</tr>
<tr>
<td>4.6</td>
<td>Liability Coverage for IRB Members</td>
<td>36</td>
</tr>
<tr>
<td>4.7</td>
<td>Reporting and Investigation of Allegations of Undue Influence</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>Human Subject Research Determination</td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td>Exempt Studies</td>
<td>37</td>
</tr>
<tr>
<td>6.1</td>
<td>Limitations on Exemptions</td>
<td>37</td>
</tr>
<tr>
<td>6.2</td>
<td>Categories of Exempt Research</td>
<td>37</td>
</tr>
<tr>
<td>6.3</td>
<td>FDA Exemptions</td>
<td>39</td>
</tr>
<tr>
<td>6.4</td>
<td>Procedures for Exemption Determination</td>
<td>39</td>
</tr>
<tr>
<td>7</td>
<td>IRB Review Process</td>
<td>40</td>
</tr>
<tr>
<td>7.1</td>
<td>Definitions</td>
<td>40</td>
</tr>
<tr>
<td>7.2</td>
<td>Expedited Review</td>
<td>41</td>
</tr>
<tr>
<td>7.2.1</td>
<td>Categories of Research Eligible for Expedited Review</td>
<td>41</td>
</tr>
<tr>
<td>7.2.2</td>
<td>Expedited Review Procedures</td>
<td>45</td>
</tr>
<tr>
<td>7.2.3</td>
<td>Informing the IRB</td>
<td>45</td>
</tr>
<tr>
<td>7.3</td>
<td>Convened IRB Meetings</td>
<td>46</td>
</tr>
<tr>
<td>7.3.1</td>
<td>IRB Meeting Schedule</td>
<td>46</td>
</tr>
<tr>
<td>7.3.2</td>
<td>Pre-Review</td>
<td>46</td>
</tr>
<tr>
<td>7.3.3</td>
<td>Reviewers</td>
<td>46</td>
</tr>
<tr>
<td>7.3.4</td>
<td>Materials received by the IRB</td>
<td>47</td>
</tr>
<tr>
<td>7.3.5</td>
<td>Quorum</td>
<td>48</td>
</tr>
<tr>
<td>7.3.6</td>
<td>Meeting Procedures</td>
<td>49</td>
</tr>
<tr>
<td>7.3.7</td>
<td>Guests</td>
<td>49</td>
</tr>
<tr>
<td>7.4</td>
<td>Criteria for IRB Approval of Research</td>
<td>49</td>
</tr>
<tr>
<td>7.4.1</td>
<td>Risk/Benefit Assessment</td>
<td>50</td>
</tr>
<tr>
<td>7.4.2</td>
<td>Equitable Selection of Participants</td>
<td>51</td>
</tr>
<tr>
<td>7.4.3</td>
<td>Informed Consent</td>
<td>52</td>
</tr>
<tr>
<td>7.4.4</td>
<td>Data and Safety Monitoring</td>
<td>52</td>
</tr>
<tr>
<td>7.4.5</td>
<td>Privacy and Confidentiality</td>
<td>54</td>
</tr>
<tr>
<td>7.4.6</td>
<td>Vulnerable Populations</td>
<td>56</td>
</tr>
<tr>
<td>7.5</td>
<td>Additional Considerations</td>
<td>56</td>
</tr>
<tr>
<td>7.5.1</td>
<td>Determination of Risk</td>
<td>56</td>
</tr>
<tr>
<td>7.5.2</td>
<td>Period of Approval</td>
<td>56</td>
</tr>
<tr>
<td>7.5.3</td>
<td>Review More Often Than Annually</td>
<td>56</td>
</tr>
<tr>
<td>7.5.4</td>
<td>Independent Verification That No Material Changes Have Occurred</td>
<td>57</td>
</tr>
<tr>
<td>7.5.5</td>
<td>Consent Monitoring</td>
<td>58</td>
</tr>
<tr>
<td>7.5.6</td>
<td>Investigator Qualifications</td>
<td>59</td>
</tr>
<tr>
<td>7.5.7</td>
<td>Investigator Significant Financial Interest / Conflicts of Interest (COI)</td>
<td>59</td>
</tr>
<tr>
<td>7.5.8</td>
<td>Institutional Conflicts of Interest</td>
<td>59</td>
</tr>
<tr>
<td>7.5.9</td>
<td>Significant New Findings</td>
<td>59</td>
</tr>
<tr>
<td>7.5.10</td>
<td>Advertisements and Recruitment Materials</td>
<td>60</td>
</tr>
<tr>
<td>7.5.11</td>
<td>Payment to Research Participants</td>
<td>61</td>
</tr>
<tr>
<td>7.5.12</td>
<td>Non-Monetary Gifts and Incentives</td>
<td>62</td>
</tr>
<tr>
<td>7.5.13</td>
<td>State and Local Laws</td>
<td>62</td>
</tr>
</tbody>
</table>
21.1 Researcher Conflicts of Interest ................................................................. 144
  21.1.1 Procedures ......................................................................................... 144
21.2 IRB Member Conflict of Interest ............................................................... 146
21.3 Institutional Conflict of Interest ................................................................. 146
21.4 Recruitment Incentives ............................................................................. 146
22 Outreach ........................................................................................................ 147
  22.1 Responsibility ......................................................................................... 147
22.2 Outreach Resources and Educational Materials ........................................... 148
22.3 Evaluation ................................................................................................ 148
23 Health Insurance Portability and Accountability Act (HIPAA) ....................... 148
  23.1 Definitions (from the NIH HIPAA Privacy Booklet for Research) .......... 149
  23.2 The IRB’s Role under the Privacy Rule .................................................. 151
  23.3 Authorization ......................................................................................... 152
  23.4 Waiver or Alteration of the Authorization Requirement .......................... 153
  23.5 Activities Preparatory to Research ........................................................ 154
  23.6 Research Using Decedent’s Information ............................................... 155
  23.7 Future Uses: Databases and Repositories ............................................. 155
  23.8 Ancillary Studies .................................................................................... 155
  23.9 De-identification of PHI under the Privacy Rule ................................... 156
  23.10 Limited Data Sets and Data Use Agreements ........................................ 157
  23.11 Research Participant Access to PHI ..................................................... 158
  23.12 Accounting of Disclosures .................................................................... 158
24 Information Security ....................................................................................... 159
25 Special Topics ............................................................................................... 160
  25.1 Community Based Research .................................................................... 160
  25.2 International Research ............................................................................ 161
  25.3 Research Repositories and Research Involving Coded Private Information or
    Biological Specimens ..................................................................................... 163
    25.3.1 Biological Specimens ........................................................................ 163
    25.3.2 Regulatory Oversight ......................................................................... 164
    25.3.3 IRB Review ......................................................................................... 164
    25.3.4 Coded Human Data or Biological Specimens .................................... 165
    25.3.5 Who Should Determine Whether Coded Private Information or Specimens
      Is Human Subjects Research ................................................................. 166
    25.3.6 Data or Biological Sample Repositories .......................................... 166
  25.4 Certificate of Confidentiality (CoC) ........................................................ 169
    25.4.1 Statutory Basis for Protection ........................................................ 169
    25.4.2 Usage ............................................................................................... 170
    25.4.3 Application Procedures .................................................................... 171
  25.5 Mandatory Reporting .............................................................................. 171
  25.6 Dartmouth Students and Employees as Research Participants ................. 172
    25.6.1 Human Subject Research and Course Projects ................................. 172
    25.6.2 Independent Study, Theses and Dissertations .................................. 173
  25.7 Oral History ............................................................................................ 174
25.8 Genetic Studies ................................................................. 174
25.9 Case Reports Requiring IRB Review .................................. 175
  25.9.1 Definitions ................................................................. 175
25.10 Research supported by the Department of Defense (DoD) .......... 176
1 Dartmouth Human Research Protection Program

The Dartmouth HRPP is comprised of the following stakeholders:

Dartmouth College: Arts & Sciences; Geisel School of Medicine; Thayer School of Engineering; Tuck Business School
And Components:
Dartmouth Hitchcock Medical Center: Mary Hitchcock Memorial Hospital; Dartmouth Hitchcock Clinic; ChaD: Children's Hospital at Dartmouth; Norris Cotton Cancer Center (NCI-funded Comprehensive Cancer Center) and affiliated clinics.

Dartmouth fosters a research environment that promotes respect for the rights and welfare of individuals recruited for, or participating in, research conducted by or under the jurisdiction of Dartmouth (See Section 1.8). In the review and conduct of research, actions by Dartmouth will be guided by the principles set forth in the Ethical Principles and Guidelines for the Protection of Human Subjects of Research (often referred to as the Belmont Report), respect for persons, beneficence and justice. The actions of Dartmouth will conform to all applicable federal, state and local laws and regulations and Institutional policies. In order to fulfill this policy, the Organization has established a Human Research Protection Program (HRPP. The Dartmouth HRPP stakeholders, in partnership with its research community, is responsible for ensuring the ethical and equitable treatment of all human research participants in research conducted under its jurisdiction. The research may be externally funded, funded by Dartmouth sources, or conducted without direct funding.

1.1 Mission

The mission of the HRPP is to:

- Safeguard and promote the health and welfare of participants in human research by ensuring that their rights, safety and well-being are protected;
- Provide guidance and support to the research community in the conduct of human research;
- Assist the research community in ensuring compliance with relevant laws and regulations;
- To provide timely and high quality education, review and monitoring of human research projects; and
- To facilitate excellence in human research.

The HRPP includes mechanisms to:

- Monitor, evaluate and continually improve the protection of human research participants;
- Dedicate resources sufficient to do so;
• Exercise oversight of research protection;
• Educate investigators and research staff about their ethical responsibility to protect research participants;
• When appropriate, intervene in research and respond directly to concerns of research participants.

1.2 Institutional Authority

Dartmouth’s HRPP operates under the authority of the Organization document “Human Research Protection Program (HRPP)”. The operating procedures in this document “...serves as the governing procedures for the conduct and review of all human research conducted under the jurisdiction of the Dartmouth.” The HRPP Document and these operating procedures are made available to all Dartmouth investigators and research staff and are posted on the HRPP website, and in the Dartmouth web-based research administration system, Rapport.

1.3 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 identical to 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 Subjects Research.** Human Subjects Research means any activity that meets the definition of “research” and involves “human subjects” as defined by either the Common Rule or FDA regulations. Note: The terms “subject” and “participant” are used interchangeably in this document.

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

For the purposes of this policy, a “systematic investigation” is an activity that involves a prospective study plan which incorporates data collection, either quantitative or qualitative, and data analysis to answer a study question. Investigations designed to develop or contribute to generalizable knowledge are those designed to draw general conclusions (i.e., knowledge gained from a study may be applied to populations outside of the specific study population), inform policy, or generalize findings.

The FDA has defined “research” as being synonymous with the term “clinical investigation”. A clinical investigation, 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 Food and Drug Administration under Sections 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act, or need not meet the requirements for prior submission to the Food and Drug Administration 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 Food and Drug Administration 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)]

Experiments that must meet the requirements for prior submission to the Food and Drug Administration 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)]

Experiments that must meet the requirements for prior submission to the Food and Drug Administration 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)]

Any activity in which results are being submitted to or held for inspection by 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)]

**Human Research Participant/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)].

- **Intervention** means both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject’s environment that are performed for research purposes.
- **Interaction** means communication or interpersonal contact between investigator and subject.
- **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).
- **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, human subject means an individual who is or becomes a participant in a clinical investigation, either as a recipient of the test article or as a control. A subject may be in normal health or may have a medical condition or disease. In the case of a medical device, a human subject/participant also includes any individual on whose specimen an investigational device is used or tested or used as a control.

**Test Article.** The FDA defines “Test article” as any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act [42 U.S.C. 262 and 263b-263n]. [21 CFR 50.3(j)]
Test articles covered under the FDA regulations include, but are not limited to:

a) **Human drugs** – The primary intended use of the product is achieved through chemical action or by being metabolized by the body. A drug is defined as a substance recognized by an official pharmacopoeia or formulary; a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; a substance (other than food) intended to affect the structure or any function of the body; a substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device. Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process.)  
   [http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm](http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm)

b) **Medical Devices** - A device is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them; intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."  
   [http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051512.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051512.htm)

c) **Biological Products** - include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources — human, animal, or microorganism — and may be produced by biotechnology methods and other cutting-edge technologies. Gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available.  
   [http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm](http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm)

d) **Food Additives** - A food additive is defined in Section 201(s) of the FD&C Act as any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristic of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use); if such substance is not Generally Recognized As Safe (GRAS) or sanctioned prior to 1958 or otherwise excluded from the definition of food additives.  
e) **Color Additives** - A color additive is any dye, pigment or substance which when added or applied to a food, drug or cosmetic, or to the human body, is capable (alone or through reactions with other substances) of imparting color. Color additives for use in food, drugs, and cosmetics require premarket approval. Color additives for use in or on a medical device are subject to premarket approval, if the color additive comes in direct contact with the body for a significant period of time. [http://www.fda.gov/Food/IngredientsPackagingLabeling/Definitions/default.htm](http://www.fda.gov/Food/IngredientsPackagingLabeling/Definitions/default.htm)

f) **Foods** - Foods include dietary supplements that bear a nutrient content claim or a health claim.

g) **Infant Formulas** – Infant formulas are liquid foods intended for infants which substitute for mother’s milk.

h) **Electronic Products** - The FDA regulates certain classes of electronic products including radiation-emitting electronic products such as microwaves and x-rays.

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

**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.

**Rapport:** The Dartmouth web-based research administration system, used for all applications to CPHS.

### 1.4 Ethical Principles

Dartmouth is committed to conducting research with regard for the welfare of human research participants. With the exception of transnational research, where consideration of alternative ethical principles may apply (See Section 25), Dartmouth upholds and adheres to the principles of *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects in Research* by the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research (1979). These principles are:

1) **Respect for Persons**, which is ensured by obtaining informed consent, consideration of privacy, confidentiality, and additional protections for vulnerable populations.

2) **Beneficence**, which is ensured by assuring that possible benefits are maximized and possible risks are minimized to all human research participants.

3) **Justice**, which is ensured by the equitable selection of research participants.
Dartmouth’s HRPP, in partnership with its research community including researchers and research staff, IRB members and chairs, IRB staff, the institutional official, employees and students, is responsible for ensuring the ethical and equitable treatment of all human participants in research conducted under its jurisdiction.

1.5 Regulatory Compliance

The HRPP is responsible for ensuring compliance with federal regulations, state law and institutional policies. All human research under the jurisdiction of Dartmouth is conducted in accordance with the policy and regulations found in the Common Rule and 21 CFR 50 and 56. The actions of Dartmouth will also conform to all other applicable federal, state, and local laws and regulations, including Department of Defense (DoD), Department of Education (DoE), Family Educational Rights and Privacy Act (FERPA) and US Department of Veterans Affairs (VA).

Research supported by the Department of Defense (DoD) is reviewed and conducted in compliance with Part 219 of Title 32 CFR, Part 980 of Title 10 USC, applicable parts of Title 21 CFR (50, 56, 312, 600, 812), DoD Instruction 3216.02, DoD Directive 3210.07, and applicable additional requirements from respective DoD component(s). When Dartmouth receives funding to conduct human subjects research, Dartmouth, at the request of DoD, will sign a DoD Addendum to its Federalwide Assurance (FWA) attesting that the institution will comply with applicable federal regulations and DoD requirements for the protection of human research participants.

Research involving the use of Protected Health Information is reviewed and conducted in accordance with the Health Insurance Portability and Accountability Act (HIPAA), 45 CFR Parts 160, 162, and 164.

Research involving the use of student educational records is reviewed and conducted in accordance with the Family Educational Rights and Privacy Act (FERPA), 34 CFR Part 99.

1.6 International Conference on Harmonization-Good Clinical Practice (ICH-GCP)

Dartmouth applies the International Conference on Harmonization (“ICH”) Good Clinical Practices (“GCP”) Guidelines (sometimes referred to as “ICH-GCP” or “E6”) to the extent that they are compatible with FDA and DHHS regulations.

1.7 Federalwide Assurance (FWA)

The federal regulations require that federally-funded human subject research only be conducted at facilities covered by a Federalwide Assurance (FWA) approved by the DHHS Office for Human Research Protections (OHRP). An FWA is an organization’s assurance to the federal government that human subject research conducted at that site is in compliance with federal regulations pertaining to the protection of human subjects. The FWA designates the Institutional Review Board that will review and oversee the research, specifies the ethical
principles under which the research will be conducted, and names the individuals who will be responsible for the proper conduct of the research.

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Federalwide Assurance#: 00003095

In its FWA, Dartmouth has opted to limit the application of the FWA to non-exempt human subject research conducted or supported by DHHS or federal agencies that have adopted the Common Rule.

1.8 Research Under the Jurisdiction of Dartmouth

Research under the jurisdiction of Dartmouth includes research conducted at Dartmouth (stakeholders listed above), conducted by or under the direction of any employee or agent of Dartmouth in connection with his or her institutional responsibilities, or conducted by or under the direction of any employee or agent of Dartmouth using any Dartmouth property or facility.

Agent. Agents include all individuals performing institutionally designated activities or exercising institutionally delegated authority or responsibility.

Engagement. The Department of Health and Human Services (HHS) regulations [45 CFR 46.103[a]] require that an institution “engaged” in human subjects research conducted or supported by a Federal Department or Agency provide the Office for Human Research Protections (OHRP) with a satisfactory assurance of compliance with the HHS regulations, unless the research is exempt under 45 CFR 46.101(b). “In general, an institution is considered engaged in a particular non-exempt human subjects research project when its employees or agents for the purposes of the research project obtain: (1) data about the subjects of the research through intervention or interaction with them; (2) identifiable private information about the subjects of the research; or (3) the informed consent of human subjects for the research.” In general, institutions that receive an award through a grant, contract, or cooperative agreement directly from HHS for the non-exempt human subjects research (i.e. awardee institutions) are also considered engaged in research even where all activities involving human subjects are carried out by employees or agents of another institution.

FDA regulations are oriented to the responsibilities of IRBs, investigators, and sponsors as opposed to institutions. In general, FDA-regulated research conducted in Dartmouth facilities or by Dartmouth Principal or Sub-Investigators (as defined on the FDA 1572 or delegation of responsibilities log) requires review by a Dartmouth-designated IRB. Exceptions to this requirement may be granted on a case-by-case basis (e.g., when Dartmouth’s involvement in the research is limited to the provision of a common diagnostic procedure and associated reading or analysis).
The IRB Office Director or designee, with the assistance of an IRB Chair, IRB Office staff and legal counsel as needed, will determine whether Dartmouth is engaged in a particular research study. Investigators and other institutions may not independently determine Dartmouth’s engagement.

When Dartmouth is engaged in research, the Institutional Official or designee may choose to enter into an agreement to cede review to an external IRB.


1.9 Written policies and procedures

Dartmouth’s Standard Operating Policies and Procedures for Human Research Protection detail the policies and regulations governing research with human participants and the requirements for submitting research proposals for review by the Dartmouth IRB. The policies and procedures are reviewed annually and revised as needed. Substantive changes are reviewed by the IRB members, Institutional Official and other stakeholder offices, as applicable, with policies and procedures revised as the need for changes are identified.

The HRPP website and stakeholders keeps Dartmouth’s research community apprised of new information that may affect the human research protection program, including laws, regulations, policies, procedures, and emerging ethical and scientific issues on its website and through campus electronic mailing lists. The policies and procedures are available on Dartmouth’s HRPP website and copies available upon request. Changes to the policies and procedures are communicated to investigators and research staff, IRB members and staff by way of electronic mail, newsletters and/or in-person in-servicing.

1.10 Dartmouth’s HRPP Structure

The HRPP consists of the following individuals and committees: Institutional Official, Director of the IRB, IRB Office staff, 5 IRB(s), Institutional Biosafety Committee, Radiation Safety Committee, Office of Research Compliance, Research Conflict of Interest Committee, Office of Sponsored Projects, Legal Counsel, investigators, research staff and investigational pharmacy staff. The objective of this system is to assist the institution in meeting ethical principles and regulatory requirements for the protection of human research participants.

The following officials, administrative units and individuals have primary responsibilities for the protection of human research participants:

1.11 Institutional Official

The ultimate responsibility of the HRPP resides with the Institutional Official (IO) of the program. The IO is legally authorized to represent Dartmouth. The IO is the signatory of the
FWA and assumes the obligations of the FWA. At Dartmouth, the Vice Provost for Research is the IO. The IO is responsible for ensuring that the Dartmouth HRPP and IRBs have the resources and support necessary to comply with all institutional policies, laws, and regulations that govern human research. Such resources include, but are not limited to:

- Staffing commensurate with the size and complexity of the research program;
- Appropriate office space, equipment, materials, and technology;
- Resources for the production, maintenance, and secure storage of HRPP and IRB records;
- Resources for auditing and other compliance activities and investigation of non-compliance;
- Access to legal counsel;
- Support for educational opportunities related to human research protections for IRB members, relevant administrative staff, and all members of the research team.
- Support for evaluation of Conflict of Interest; and
- Support for Community Outreach.

The IO conducts ongoing reviews of HRPP and IRB function and requirements and a yearly review of resources and makes adjustments as needed.

The IO is also responsible for:

- Fostering, supporting and maintaining an institutional culture that supports the ethical conduct of all human research and the adherence to regulations and institutional policies;
- Ensuring that the IRBs function independently by, among other mechanisms, being directly accessible to the IRB Chair(s) and members if they experience undue influence or if they have concerns about the function of the IRB;
- Oversight of the Institutional Review Board (IRB);
- Oversight over the conduct of research conducted by all Dartmouth investigators;
- Assuring that IRB members are appropriately knowledgeable to review research in accordance with ethical standards and applicable regulations;
- Assuring that all investigators are appropriately knowledgeable to conduct research in accordance with ethical standards and applicable regulations; and
- Oversight of the development and implementation of an educational plan for IRB members, staff and investigators.

The Dartmouth IO must complete appropriate training on human research protections [for example CITI]. The IRB Office provides on-going continuing education for the IO concerning human research protections.
The IO is made known to employees of the organization and is accessible by phone, email, in person or other methods of communication. The IRB Chairmen and IRB Office Director have direct access to the IO for any concerns or issues related to the HRPP.

In the performance of these duties, the IO has the authority to delegate such activities as may be necessary in order to effectively administer the program. However, the IO is ultimately responsible and is expected to be knowledgeable about all human research protections responsibilities at the organization.

1.12 IRB Office Director

The IRB Office Director reports to the IO and is responsible for:

1. Developing, managing and evaluating policies and procedures that ensure compliance with all state, and federal regulations governing research, this includes monitoring changes in regulations and policies that relate to human research protection and overseeing the administration of the IRB;

2. Advising the IO on key matters regarding research at Dartmouth;

3. Implementing Dartmouth’s HRPP policies and procedures;

4. Submitting, implementing and maintaining an approved FWA through the IO and the U.S. Department of Health and Human Services Office for Human Research Protections (OHRP);

5. Managing the finances of Dartmouth’s IRB Office and IRBs;

6. Assisting investigators in their efforts to carry out Dartmouth’s research mission;

7. Developing and implementing needed improvements and ensuring follow-up of actions, as appropriate, for the purpose of managing risk in the research program;

8. Developing training requirements as required and as appropriate for investigators, committee members and research staff, and ensuring that training is completed on a timely basis;

9. Serving as the primary contact at Dartmouth for the Office for Human Research Protections (OHRP) of the U.S. Department of Health and Human Services, the Food & Drug Administration (FDA) and other federal regulatory agencies;

10. Day-to-day responsibility for the operation of the IRB Office, including supervision of staff;

11. Responding to questions regarding the protection of human research participants;

12. Working closely with the IRB Chairs on the development of policy and procedures, as well as organizing and documenting the review process.
1.13 IRB Staff

In addition to the leadership structure described above, other support staff members for the IRB Office and IRBs include IRB Office Director, Associate Director, Senior Analysts (including an Education Specialist), Program Coordinator, Administrative Assistant. The duties and responsibilities for all staff are found in their respective job descriptions, and their performance is evaluated on an annual basis. The Dartmouth IRB Office staff reports to the IRB Office Associate Director, who has day-to-day responsibilities for its operations.

1.14 Institutional Review Board (IRB)

Dartmouth has 5 on-site IRBs, with members recommended by the IRB Chairs and appointed by the Dartmouth IO. The IRB prospectively reviews and makes decisions concerning all human research conducted at Dartmouth facilities, by its employees or agents, or under its jurisdiction unless another IRB has been designated by Dartmouth to do so. The IRB is responsible for the protection of rights and welfare of human research participants at Dartmouth, through review and oversight of safe and ethical research. It discharges this duty by complying with the requirements of federal and state regulations, the FWA, and institutional policies. (See Section 4 for a detailed discussion of the IRB.)

The IRB functions independently of, but in coordination with, other institutional committees and officials. The IRB, however, makes an independent determination whether to approve or disapprove a research plan based upon whether or not human research participants are adequately protected.

Research that has been reviewed and approved by the IRB may be subject to review and disapproval by officials of the institution. However, those officials may not approve human research that has not been approved or has been disapproved by the IRB.

Dartmouth also uses the services of several external IRBs. Including several academic medical centers (e.g. Harvard Catalyst) as well as the NCI IRB, Quorum, WIRB, Chesapeake, Sterling and other commercial IRBs.

1.15 Legal Counsel’s Office

The Dartmouth HRPP relies on its Legal Counsel at Dartmouth College and Dartmouth-Hitchcock Medical Center for the interpretation and application of state law and the laws of any other jurisdiction where Dartmouth research is conducted, as they apply to human research. Legal Counsel will also advise the IRB about other legal issues such as who is a child, and who can serve as a legally authorized representative or guardian. When there are any conflicts between federal or national law and other applicable laws, the Legal Counsel will determine the appropriate resolution.
1.16 Department Chairs and/or Institutional Leaders

Department Chairs, and institutional leaders when the Department Chair is the PI, are responsible for ensuring that the PI is qualified by training and experience to conduct the proposed research. For each research study submitted to Dartmouth’s IRB for review, the department chairman or leader must certify that he/she accepts responsibility for supporting adherence to the federal and state regulations and institutional policies governing the protection of human research participants, including applicable institutional credentialing requirements. Department chairs/leaders are responsible for assuring that investigators have the resources required to conduct the research in a way that will protect the rights and welfare of research participants. Such resources include, but are not limited to, personnel, space, equipment and time.

Department chairs/leaders are required to review all proposals before they are submitted to the IRB for review. The signature of the Department chair or leader indicates that (1) the PI is qualified and has the necessary resources to safely conduct the study, and (2) attests to the scientific merit of a study, which means

- The research uses procedures consistent with sound research design;
- The research design is sound enough to reasonably expect the research to answer its proposed question.

1.17 The Investigator

The investigator is ultimately responsible for the protection of human research participants. The investigator is expected to abide by the highest ethical standards and develop a research plan that incorporates the principles of the Belmont Report. He/she is expected to conduct research in accordance with the IRB approved research plan and to oversee all aspects of the research by providing training and supervision of support staff, including oversight of the informed consent process. All participants must give informed consent unless the requirement has specifically been waived by the IRB. The investigator must establish and maintain an open line of communication with research participants within his/her responsibility. In addition to complying with all the policies and standards of the governing regulatory bodies, the investigator must comply with institutional and administrative requirements for conducting research. The investigator is responsible for ensuring that all research staff complete all institutional required training as well as training for their responsibilities in any given specific research study. When investigational drugs or devices are used, the investigator is responsible for having a plan for their storage, security, dispensing, accounting, and disposal.

1.18 Other Related Units

1.18.1.1 Office of Sponsored Projects (OSP at Dartmouth College); Clinical Trials Office (CTO at Dartmouth-Hitchcock Medical Center)

Research agreements are reviewed by either the OSP or CTO to ensure compliance with federal, foundation, or non-profit sponsors. This institutional review also ensures that all terms
of the award are in compliance with institutional policies. Only designated senior individuals have the authority to approve research proposals and to execute research agreements on behalf of the institution.

The contracts administrator also have access to the IRB submission to confirm that the contract and the consent document(s) are consistent in terms of costs to research participants and the party responsible for payment in case of injury.

When the grant or contract agreement includes human research activities that will be conducted by investigators who are not employees or agents of Dartmouth, a subcontract is executed between Dartmouth and the collaborating institution. The subcontract includes the requirement for the collaborating institution to assure compliance with federal regulations for the protection of human research participants and to provide documentation of current and ongoing IRB approval. The collaborating institution must also ensure that key personnel involved in human research are in compliance with the NIH policy on education in the protection of human research participants and provide documentation of education of key personnel to Dartmouth when NIH is funding the study.

1.18.1.2 Investigational Pharmacy at Dartmouth-Hitchcock (D-H) Medical Center

Investigators provide the Investigational Pharmacy with complete information about all IRB approved research that takes place at Dartmouth-Hitchcock and under its jurisdiction. The Investigational Pharmacy assures that information about all studies involving drugs used in research is shared with Pharmacy Staff as appropriate.

The D-H Investigational Pharmacy is responsible for storing, accounting for, dispensing, and compounding of most investigational drugs used in research, whether conducted inpatient or outpatient. The manufacture/compounding of drug products not commercially available is coordinated by the Investigational Pharmacy. Waivers from use of the D-H investigational pharmacy for handling investigational drugs are considered on a case by case basis with required information regarding storage, accounting and dispensing.

The D-H Investigational Pharmacy is available to provide guidance to investigators on the management of study drugs.

1.18.1.3 Compliance

Dartmouth’s Office of Research Compliance has a Research Compliance Officer that supports the research mission of Dartmouth. The Director of the Research Compliance Office reports to Dartmouth’s Vice Provost for Research. The Office of Research Compliance serves as a resource for Dartmouth’s IRB Office, the IRBs and individual investigators and research staff; provides education and training; facilitates the development of system-wide research policies and procedures; manages study audits and ensures post-approval monitoring of all human research studies and coordinates and monitors research management activities for compliance with federal, state and local laws and regulations and institutional policies. In addition, the Clinical Trials Office at Dartmouth-Hitchcock Medical Center has a monitoring component.
1.1.1.4 Relationship Among Components

The Institutional Official, Office of Sponsored Projects, Clinical Trials Office and the Office of Research Compliance have access to the IRB Office database, Rapport, and study specific information. Copies of IRB approval letters and expiration notices are available to the Institutional Official, Office of Sponsored Projects, Clinical Trials Office, Office of Research Compliance and applicable Department Chair as applicable.

Dartmouth has a Council on Sponsored Activities (CSA) charged with fostering excellence in research and research training, to assist with strategic planning for research development and research facilities, and to provide recommendations to the Vice Provost for Research. The CSA, chaired by the Vice Provost for Research or designee, meets quarterly. Legal, Sponsored Projects, Investigators, institutional leadership and research compliance committees are represented at its meetings.

1.19 Protocol-Specific Coordination

In addition to IRB approval, an Investigator must obtain and document the approval, support, or permission of other individuals and departments or entities impacted by the research and approval by other oversight committees, as applicable, including, but not limited to:

- D-H Medical Center and affiliates
- Investigational Pharmacy
- Nursing
- Permission to enter classrooms or hospital units
- Permission from external research locations (sites)
- Departmental approvals
- Database access permissions
- Institutional Biosafety Committee
- Radiation Safety Committee
- Conflict of Interest

The IRB may request review or consultation with any of the above listed or other organizational committees or components even when such review or consultation is not required by policy.

Other committees and officials may not approve human research to commence that has not been approved by or that has been disapproved by the IRB.
1.20 Collaborative Research Projects

In the conduct of collaborative research projects, Dartmouth acknowledges that each organization is responsible for safeguarding the rights and welfare of human research participants and for complying with applicable federal regulations. For IRB review, Dartmouth may choose to enter into a joint review arrangement, rely on the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort. A formal relationship must be established between Dartmouth and the other institution through an Institutional Agreement, a Memorandum of Understanding, Reliance Agreement or other such written agreement. This relationship must be formalized before Dartmouth will accept any human research proposals from the other institution or rely on the review of the other institution.

When the Dartmouth IRB reviews research conducted in whole or in part at another institution, the particular characteristics of each institution’s local research context must be considered, either (i) through member knowledge of local research context or (ii) through the use of consultants or other sources of information.

Before a collaborative study can begin, it must be approved by the IRB of record for the lead or coordinating facility. Before the study can begin at a participating facility, it must be approved by the IRB of record for the participating facility and, when required, the IRB of record for the lead or coordinating facility.

For collaborative research when the Dartmouth investigator is the lead investigator, or when Dartmouth is the coordinating facility for a research study, the investigator must identify all institutions participating in the research, the responsible IRB(s), and the procedures for dissemination of study information (IRB initial and continuing approvals, relevant reports of unanticipated problems, study modifications, and interim reports) among all participating institutions. The investigator is responsible for serving as the liaison with regulatory and funding agencies, with other participating facilities, and for all aspects of internal review and oversight procedures. The investigator is responsible for ensuring that all participating facilities obtain review and approval from their IRB of record initially, for all modifications to the research plan, and for continuing review. The investigator is responsible for ensuring that the research study is reviewed and approved by any other applicable committees (e.g., Biosafety) at the lead or coordinating facility and at the participating facilities prior to enrollment of study participants.

The investigator should follow these procedures when Dartmouth is the lead or coordinating facility as applicable:

• During the initial IRB submission of the multi-site study, the investigator indicates in the application form or in an application letter that Dartmouth is the lead or coordinating facility of a multi-site study.
  • The investigator submits the following information with the IRB application:
    • Name of each participating facility
    • Confirmation whether or not each participating facility has an FWA (including FWA number and expiration date)
    • Contact name and information for investigator/s at each participating facility
Contact name and information for IRB of record at each participating facility

The IRB Reliance Agreement (signed by the PI) should indicate roles and responsibilities including:

- Assuring all participating facilities have the most current version of the research plan
- Confirming that all modifications to the research plan are communicated to participating sites
- Communicating to participating facilities any serious adverse events and unanticipated problems involving risks to subjects or others
- Communicating interim analyses, including data safety reviews, to participating facilities, as applicable
- Communicating regularly with participating sites about the progress of the study

- Plan for monitoring the conduct of the research at participating facilities, as applicable
- The investigator maintains an approval letter for each site from the individual site’s IRB of record upon receipt. Following approval from Dartmouth, research activities may commence at each site unless Dartmouth’s IRB has determined otherwise.
- The investigator maintains documentation of all correspondence between participating sites and their IRB of record.

When Dartmouth is engaged in only part of a collaborative research project, and Dartmouth is not the lead or coordinating site, the Dartmouth IRB may choose to only review and approve the part(s) of the research in which the Dartmouth investigator is engaged. For example, if Dartmouth is operating the statistical center for a multicenter trial that receives identifiable private information from multiple other institutions, the Dartmouth IRB reviews and approves the research activities related to the receipt and processing of the identifiable private information by the statistical center.

2 Quality Improvement

Dartmouth performs Quality Improvement activities for the purposes of monitoring the safety of ongoing studies and measuring and improving human research protection effectiveness, quality, and compliance with organizational policies and procedures and applicable federal, state, and local laws.

2.1 External Monitoring, Audit, and Inspection Reports

All reports for clinical research from external monitors, auditors, or inspectors are maintained by the investigators. In the Norris Cotton Cancer Center (NCCC) all external monitoring reports are also maintained and reviewed by the NCCC central compliance team in the Office of Clinical Research (OCR). Issues or concerns which could impact the rights or welfare of human research participants or issues indicative of possible serious or continuing noncompliance are submitted
to the CPHS Office. If such issues are identified, the report is forwarded to the convened IRB to determine what additional actions are necessary.

2.2 Investigator Compliance Reviews

The Clinical Trials Office (CTO) and the NCCC conduct post-approval directed (“for cause”) monitoring and periodic (not “for cause”) compliance monitoring of clinical investigator research plans. Additionally, the CTO, NCCC, or the CPHS may appoint a subcommittee for the purpose of conducting a for-cause or not for-cause monitoring program of one or more research plans under its jurisdiction.

Compliance reviews are conducted to assess clinical investigator compliance with federal, state, and local law, the IRB-approved protocol and Dartmouth’s policies, and to identify areas for improvement, and to provide recommendations based on existing policies and procedures. The results of compliance reviews are reported to the investigator and department chair with a follow up plan prescribed in the report. If it is identified that research participants have been exposed to unexpected serious harm, the reviewer promptly reports such findings to the IRB Office/Chair for immediate action.

Compliance reviews may include:

a) Requesting progress reports from investigators;
b) Examining investigator-held research records;
c) Contacting research participants;
d) Observing sites where research involving human participants and/or the informed consent process is being conducted;
e) Reviewing advertisements and other recruiting materials;
f) Reviewing projects to verify from sources other than the investigator that no unapproved changes have occurred since previous review;
g) Assuring that the consent document(s) includes the appropriate information and disclosures about conflicts of interest;
h) Assuring that the consent document includes all required elements for HIPAA authorization;
i) Conducting other monitoring or auditing activities as deemed appropriate by the IRB or IRB.

2.3 IRB Compliance Reviews

The IRB Director is responsible for producing regular reports on IRB Office operations regarding the volume of review actions in various categories and interval analyses of the length of time each action requires. The IRB Director, Chairs, and IO evaluate these reports as needed to assist efforts to facilitate the efficiency and effectiveness of research administration.
An experienced monitor or consultant periodically reviews the activities of the IRB to assess compliance with regulatory requirements and to identify areas for improvement; this includes a review of IRB records including:

a) Review of the IRB minutes to determine that adequate documentation of the meeting discussion has occurred. This review includes assessing the documentation surrounding the discussion for protections of vulnerable populations as well as risk/benefit ratio and consent issues that are included in the criteria for approval;
b) Review of the IRB minutes to assure that quorum was met and maintained;
c) Review of IRB documentation, including IRB minutes, to assess whether privacy provisions, according to HIPAA, have been adequately reviewed, discussed and documented;
d) Evaluating the continuing review discussions to assure they are substantive and meaningful and that, in the event of a lapse, no study activities took place;
e) Reviewing IRB files to assure retention of appropriate documentation and consistent organization of the IRB file according to current policies and procedures;
f) Reviewing the IRB database to assure all required fields are completed accurately;
g) Verifying IRB approvals for collaborating institutions or external performance sites;
h) Reviewing the appropriate metrics (for example, time from submission to first review) to evaluate the quality, efficiency, and effectiveness of the IRB review process; and
i) Other monitoring or auditing activities deemed appropriate.

Results of IRB compliance reviews are reported to the Institutional Official, IRB Chairs and IRB Director. If any deficiencies are noted in the review, a corrective action plan is developed by the Director and Chairmen and approved by the Institutional Official. The Director has responsibility for implementing the corrective action plan, the results of which are evaluated by the Institutional Official.

2.4 HRPP Quality Assessment and Improvement

Meetings of the Institutional Official (or designee), IRB Director (or designee) and other key stakeholders in the HRPP including but not limited to the Directors of the Office of Sponsored Projects (OSP), Clinical Trials Office (CTO), Norris Cotton Cancer Center (NCCC)/ Office of Clinical Research (OCR), Technology Transfer Office (TTO), SYNERGY (Clinical Translational Science Award - CTSA), Environmental Health & Safety (EHS), and the Research Compliance Officer, are held during which quality improvement is discussed with intent to assess compliance and achieve targeted levels of quality, efficiency, and effectiveness of the HRPP (e.g., continuous investigator training; use of IRB-approved consent forms, turn-around time of exemption determinations, etc.). The discussions include:

- Goals with respect to measuring effectiveness, identifying opportunities for improvement and achieving and maintaining targeted levels of quality, efficiency, effectiveness and compliance
- Methods to assess compliance and make improvements
- Methods to assess quality, efficiency, or effectiveness and make improvements
Results of the discussions are reviewed by the Institutional Official. If problems are identified and changes required, stakeholders collaborate, as needed, in the development of a corrective action plan, its implementation, and evaluation of its effectiveness.

In addition, within the Office of Clinical Research Structure and Support, several areas include on-going quality improvement functions including:

- **Clinical Cancer Review Committee (CCRC)**
  Provides required peer review of scientific merit prior to IRB review. Reviews clinical research protocols for treatment, prevention, control or intervention of cancer and protocol amendments

- **NCCC Data, Safety Monitoring, and Accrual Committee (DSMAC)**
  Provides required peer review of clinical research protocols for which a Dartmouth investigator is both investigator and sponsor of the protocol. Review toxicity patterns, data integrity, protocol adherence, and progress toward study objectives. Reviews study accrual.

- **Clinical Trials Investigational Order Set Committee (CTIOSC)**
  Provides required review of drug order sets for clinical trials prior to study activation

- **Cancer Clinical Research Quality Improvement Committee (QIC)**
  Focuses on continuous clinical research process improvement at the Norris Cotton Cancer Center. Analyzes trends in the quality of research by quarterly reviews of protocol deviation reports, local serious adverse event reports, ongoing corrective and preventative actions plans, reports from research ancillary support services, and reports from PIs, NPs, Clinical Research Coordinators, Research Nurses, Regulatory staff, and administrators.

### 3 Education

#### 3.1 Ongoing Education of IRB Chairman, Members, and Staff

Recognizing that a vital component of a comprehensive human research protection program is an education program, Dartmouth is committed to providing training and an on-going educational process for IRB members and the staff of the IRB and stakeholders of the HRPP, related to ethical concerns and regulatory and organizational requirements for the protection of human research participants.

**Orientation**

New IRB members, including alternate members, meet with IRB Office staff for an orientation session. At the session, the federal regulations are reviewed and an orientation to IRB processes given. Each new member receives a copy of:

- The Belmont Report;
- Institutional Review Board Member Handbook (Amdur and Bankert);
- Federal regulations relevant to the IRB.

New members are required to complete the Initial Education requirement for IRB members before they may join as a voting member.
Initial Education

IRB members and IRB Office administrators and staff complete the required modules in the CITI Course in the Protection of Human Research Subjects (biomedical and social behavioral track), including the IRB Member Module - “What Every New IRB Member Needs to Know” and the module on Conflicts of Interest. Community members are expected to review the “I Have Agreed to be an IRB Community Member. Now What?” module as well.

Continuing Education

To ensure that oversight of human research is ethically grounded and the decisions made by the IRB are consistent with current regulatory and policy requirements, training is continuous for IRB members throughout their service on the IRB.

IRB members and IRB Office administrators and staff must satisfy continuing education requirements on an annual basis. Dartmouth uses the following activities as a means for offering continuing education to IRB members and IRB Office administrators and staff including but not limited to:

- In-service training at IRB meetings;
- Training workshops;
- Copies of appropriate publications;
- Identification and dissemination by the Director of new information that might affect the human research protection program, including laws, regulations, policies, procedures, and emerging ethical and scientific issues to IRB members via email, mail, or during IRB meetings; and
- Unlimited access to the IRB Office resource library.

The activities for continuing education vary on a yearly basis depending on operating budget and areas of need, as determined by the Director.

Each year the Institutional Official (IO) provides support for as many members of the CPHS and Office staff as possible to attend the PRIM&R AER conference or regional OHRP conferences on human research protections.

3.2 Ongoing Education of Investigators and Research Team

Another vital component of a comprehensive human research protection program is an education program for all individuals involved with human research participants. Dartmouth is committed to providing training and an on-going educational process for investigators and members of their research team related to ethical concerns and regulatory and organizational requirements for the protection of human research participants.
3.2.1 Initial Education

Investigators, key personnel, and other members of the research team must complete Dartmouth required core modules in the CITI Course in the Protection of Human Research Subjects including the modules on Conflicts of Interest, or an equivalent educational session. Evidence of current training (date of completion within 3 years of application date) for each member of the research team must be included in every new research study application and application for continuing review.

The IRB will not approve a new research plan until the initial education requirement has been completed.

Research plans and applications for continuing review and amendments are accepted and reviewed if the investigator training requirements are current, but co-investigators and members of the research team who have not yet completed the initial requirement may not participate in the study until the requirement has been met.

The Office of Clinical Research (OCR) within the Norris Cotton Cancer Center (NCCC) requires Good Clinical Practice education as offered through CITI for all clinical researchers.

Waiver of Initial Education

If individuals can provide documentation verifying that they have successfully completed human subject research training equivalent to that required by Dartmouth they may request a waiver of the requirement for Dartmouth’s Initial Education. The IRB Office staff and Director review the documentation and determine if it satisfies organizational standards. However, all investigators and members of their research team must complete the requirements for Continuing Education as described below.

3.2.2 Continuing Education and Recertification

Investigators, key personnel, and other members of a clinical research team must meet Dartmouth’s continuing education requirement every three (3) years after certification of Initial Education for as long as they are involved in research with human participants. There is no exception to this requirement. Dartmouth requires completion of appropriate refresher modules at the CITI web-based training site. Other training may be acceptable. In these cases the investigator should check with the IRB Office for a determination.

Evidence of CITI education status is validated within the IRB application, (new, continuing review and amendments). New research plans and applications for continuing review and amendments are not reviewed until the Principal Investigator’s continuing education is up to date. Co-Investigators and members of the research team whose educational requirements are not up to date may not participate in the study until the CITI requirements are current.

Investigators who are also IRB Chairmen, IRB members, or IRB Office staff must satisfy the training requirements for IRB members and staff described in this policy under Section 3.1.
4 Institutional Review Board

Dartmouth has established five Institutional Review Boards (IRB) to ensure the protection of human research participants conducted under the jurisdiction of Dartmouth. All non-exempt human research conducted under the jurisdiction of Dartmouth must be reviewed and approved by the Dartmouth IRB, or another IRB with a signed reliance agreement with Dartmouth and approval from the IRB Office prior to the initiation of the research.

Although Dartmouth has multiple IRBs to fulfill the review and oversight function, all on-site IRBs follow the same policies and procedures. For the purposes of this document, all on-site IRBs are referred to as the Dartmouth IRB.

Dartmouth also uses the services of external IRBs, including but not limited to:

- Commercial and independent IRBs including WIRB/WCG, Quorum, Schulman: this option is available to Dartmouth investigators for industry-initiated, industry-sponsored studies where WIRB has been identified by the industry sponsor as the reviewing IRB
- NCI’s Adult CIRB: for applicable cooperative oncology group protocols/studies involving adult
- NCI’s Pediatric CIRB: for applicable cooperative oncology group protocols/studies involving minors
- Academic Medical Centers: Including consortiums : IRBSmart, Catalyst, IRBRely

The authorized external IRBs that serve as the IRB-of-record for Dartmouth have the same authority as the on-site IRBs. All determinations and findings of the authorized external IRB acting in its capacity as the IRB-of-record for a study conducted at Dartmouth are equally binding on the specific study at Dartmouth.

4.1 IRB Authority

The IRB derives its authority from Dartmouth policy, as cited in Section 1.2. Under the federal regulations, IRBs have the authority:

1. To approve, require modifications to secure approval, or disapprove all human research activities overseen and conducted under the jurisdiction of Dartmouth;

2. To require that informed consent be obtained and documented in accordance with regulatory requirements unless the criteria for the waiver or alteration of such requirements has been satisfied and approved by the IRB. The IRB may require that information, in addition to that specifically mentioned in the regulations, be given to research participants when, in the IRB’s judgment, the information would meaningfully add to the protection of the rights and welfare of participants;

3. To conduct continuing review of research at intervals appropriate to the degree of risk of the research, but not less than once per year;
4. To suspend or terminate approval of research not being conducted in accordance with the IRB’s requirements or that has been associated with unexpected serious harm to participants;

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

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

The IRB functions independently. Attempts to coerce or otherwise unduly influence the actions of the IRB are forbidden by policy, and are to be reported as described in Section 4.7. Likewise, the IRB must remain free from the influence of financial and other organizational interests. No individual with responsibility for the business and financial interests of the organization may serve on the IRB.

Research that has been reviewed and approved by the IRB may be subject to review and disapproval by officials of the organization. However, those officials may NOT approve research if it has not been approved or has been disapproved by the IRB. Reviewing officials may strengthen requirements and/or conditions, or add other modifications before approval or may require approval by an additional ancillary committee. Previously approved research proposals and/or consent forms must be re-approved by the IRB before initiating any changes or modifications that result from such additional reviews/approvals.

4.2 Roles and Responsibilities

4.2.1 IRB Chair

Dartmouth’s Institutional Official (IO), in consultation with the Director of the IRB Office, appoints the IRB Chair.

The IRB Chair should be a highly respected individual, from within Dartmouth, fully capable of managing the IRB, and the matters brought before it with fairness and impartiality. The task of making the IRB a respected part of the research community falls primarily on the shoulders of the Chair. The IRB must be perceived to be fair, impartial and immune to pressure by administration, the investigators whose research plans are brought before it, and other committees and professional and nonprofessional offices/sources.

The IRB Chair is responsible for conducting the meetings and conducting expedited reviews, and may designate other experienced IRB members to perform duties such as expedited reviews and other IRB functions.

The IRB Chair is authorized to take immediate action to suspend a study or studies if information is presented regarding participant safety or for any other reason where such action would be deemed appropriate. Such action requires subsequent notice to and review by the convened IRB.

The IRB Chair advises the Institutional Official and the Director of the IRB Office about IRB member performance and competence.
The IRB Chair designates experienced IRB members who may conduct review using the expedited procedure. The designations are made on an on-going basis as new CPHS members complete applicable education requirements.

The performance of the IRB Chair is reviewed on an annual basis by the Director of the IRB Office in consultation with the Institutional Official. Feedback of this review is provided to the Chair. If the Chair is not acting in accordance with the IRB’s mission, or following these policies and procedures, has an undue number of absences, or not fulfilling the responsibilities of the Chair, he/she may be removed.

4.2.2 IRB Members

The role of an IRB member is to ensure that human research activities comply with federal regulations, state and local laws, and organizational policies and procedures, by:

1. Completing member education and training, both initial and on-going (See Section 3.1).
2. Maintaining the confidentiality of IRB deliberations and research review by the IRB.
3. Conducting and documenting reviews of assigned research in a timely fashion.
4. Attending IRB meetings as scheduled.

Members are expected to attend a minimum of 65% of all meetings. If a member is unable to attend a scheduled meeting, they inform the IRB administrative staff.

If an IRB member is to be absent for an extended period of time, he/she is expected to notify the IRB administrative staff in advance. If the member has a designated alternate, the alternate can serve during the primary member’s absence. If the member does not have a designated alternate and the member’s area of expertise is needed and not represented by another member, an alternate for the absent member may be obtained.

5. Recusing self from discussion and vote when he/she has a conflict of interest. The member may be asked to return during deliberations to answer questions or provide additional information.
6. Participating in subcommittees of the IRB if requested and available.
7. Conduct himself/herself in a professional and collegial manner.

IRB members who have completed the orientation process and have voted at one or more convened meetings may conduct review using the expedited procedure. The designations occur on an on-going basis as new CPHS members complete applicable education requirements.

Members become eligible to conduct expedited reviews after completing the orientation and voting at one or more convened meetings.

An experienced member has received education specifically related to the Criteria required for IRB approval and has served as a Full Committee member. Per DHHS and FDA regulations: The
reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. In general, CPHS members are assigned to review studies in their area of expertise, however all expedited reviewers understand the primary role of protecting the rights and welfare of research subjects.

The performance of IRB members is reviewed on an annual basis by the IRB Chair and the Director of the IRB Office. Feedback of this review is provided to the member. Members who are not acting in accordance with the IRB's mission or not following policies and procedures or who have an undue number of absences may be removed.

4.2.3 Alternate IRB members

The appointment and function of alternate IRB members is the same as that for primary IRB members. An alternate’s expertise and perspective should be comparable to those of the primary member. The role of the alternate member is to serve as a voting member of the IRB when the regular member is unavailable to attend a convened meeting. When an alternate member substitutes for a primary member, the alternate member receives and reviews the same materials prior to the IRB meeting that the primary member received.

The IRB roster identifies the primary member(s) or class of members (e.g., physician scientist) for whom each alternate member may substitute. The alternate member is not counted toward meeting quorum as a voting member unless the primary member is absent. The IRB minutes document when an alternate member replaces a primary member.

Experienced alternate members may be designated by the Chair to conduct expedited reviews.

4.2.4 Subcommittees of the IRB

The IRB Chair, in consultation with the IRB Office Director, may appoint IRB members to a subcommittee of the IRB to perform duties, as appropriate, and undertake other IRB functions, and to make recommendations to the IRB (e.g., to supplement the IRB’s initial review, continuing review, review of modifications, and/or review of reports of unanticipated problems or of serious or continuing non-compliance). The number and composition of the IRB Subcommittee shall depend on the scope of duties delegated by the IRB Chair to such IRB Subcommittee (e.g., making recommendations, conducting an inquiry, etc.). Any such Subcommittee cannot approve research that requires approval at a convened IRB meeting.

4.3 IRB Membership

The structure and composition of the Dartmouth IRB is appropriate to the amount and nature of the research that is reviewed. Every effort is made to have member representation with an understanding of the areas of specialty that encompasses most of the research performed at Dartmouth.

The IRB includes members who are knowledgeable about and experienced working with vulnerable populations that typically participate in Dartmouth research.
The IRB must promote respect for its advice and counsel in safeguarding the rights and welfare of human research participants; and possess the professional competence necessary to review specific research activities. Dartmouth has procedures (See Section 7.4.1.1) that specifically outline the requirements for review of research plans by individuals with appropriate scientific or scholarly expertise. A member of the IRB may fill multiple membership position requirements for the IRB.

Individuals from Dartmouth’s Office of Sponsored Projects, Clinical Trials Office or Office of Technology Transfer may not serve as members of the IRB or carry out day-to-day operations of the review process. Individuals from these offices may provide information to the IRB and attend IRB meetings as invited guests.

4.4 Composition of the IRB

1. The IRB has at least five members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the organization.

2. The IRB is sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and 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.

3. In addition to possessing the professional competence necessary to review specific research activities, the IRB includes members able to ascertain the acceptability of proposed research in terms of organizational commitments and regulations, applicable law, and standards of professional conduct and practice.

4. If the IRB regularly reviews research that involves a vulnerable category of people (e.g., children, prisoners, pregnant women, or handicapped or mentally disabled persons), consideration is given to the inclusion of one or more individuals on the IRB, who are knowledgeable about and experienced in working with these populations.

5. Every effort is made to ensure that the IRB does not consist entirely of men or entirely of women, including the organization's consideration of qualified persons of both sexes, so long as no appointment is made to the IRB solely on the basis of gender. The IRB does not consist entirely of members of one profession.

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

7. The IRB includes at least one member who is not otherwise affiliated with the organization and who is not part of the immediate family of a person who is affiliated with the organization.

8. The IRB includes at least one member who represents the general perspective of participants.

9. One member may satisfy more than one membership category.

10. The IRB Chairs are voting members of the IRB.
The IRB Chair and the IRB Office Director shall review the membership and composition of the IRB annually to determine if they continue to meet regulatory and organizational requirements.

4.4.1 Appointment of Members to the IRB

When the IRB Chair or the IRB Office Director identifies the need for a new, replacement, or alternate member and then identifies a candidate, they send the names of candidates to the IRB Office. Department Chairmen and others may forward nominations to the IRB Chair, IO or to the IRB Office Director.

The final decision in selecting a new member is made by the Institutional Official, in consultation with, the IRB Chair and the IRB Office Director.

Appointments are made by the Dartmouth Vice Provost of Research, for a term of 3 years. Members may resign by written notification to the IRB Chair, Vice Provost for Research or IRB Office Director.

The IRB Chair and IRB Office Director shall review the membership and composition of the IRB annually to determine if they continue to meet regulatory and institutional requirements.

4.4.2 IRB Registration Updates

Changes in IRB membership are reported to FDA and OHRP as follows:

1. A Dartmouth decision to disband a registered IRB that it is operating are reported in writing within 30 days after permanent cessation of the IRB’s review of DHHS-conducted or supported research.

2. If an FDA-regulated IRB decides to review additional types of FDA-regulated products (e.g., to review device studies if it only reviewed drug studies previously) or to discontinue reviewing clinical investigations regulated by FDA, it is reported within 30 days of the change.

3. Within 90 days after changes regarding the contact person who provided the IRB registration information or the IRB Chair.

4. To register any additional IRB before it is designated under an FWA and reviews research conducted or supported by DHHS or regulated by FDA.

5. Within 90 days of a change in the membership roster if that IRB is designated under an FWA.

4.5 Use of Consultants

When necessary, the IRB Chair, IRB members or the IRB Office Director may solicit individuals from the organization or the research community with competence in special areas to assist in the review of issues or research plans, which require scientific or scholarly expertise beyond or in addition to that available on the IRB. The IRB Office ensures that all relevant materials are provided to the outside reviewer prior to the convened meeting.
Written statements from consultants are kept in the IRB study records. Key information provided by consultants at meetings is documented in the minutes.

Consultants are subject to Dartmouth’s Conflict of Interest Policy and must confirm that they do not have a conflict of interest prior to review. Individuals who have a conflict of interest or whose spouse or immediate family member(s) has a conflict of interest in the research, including any relationship to the sponsor, are not invited to provide consultation.

The consultant’s findings are presented to the convened board for consideration either in person or in writing. If in attendance, the consultant may assist in the deliberation, but may not participate in the vote.

Ad hoc or informal consultations requested by individual members (rather than the convened board) are processed by the IRB Office in a manner that protects the investigator’s confidentiality and is in compliance with the IRB conflict of interest policy.

### 4.6 Liability Coverage for IRB Members

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

### 4.7 Reporting and Investigation of Allegations of Undue Influence

If an IRB Chair, member, or staff person feels that the IRB has been unduly influenced by any party, he/she shall make a confidential report to the IRB Office Director or IO, depending on the circumstances. Undue influence means attempting to interfere with the normal functioning and decision making of the IRB or to influence an IRB member, staff, or any other member of the research team outside of the established processes or normal and accepted methods in order to obtain a particular result, decision or action by the IRB or one of its members or staff.

The IRB Office Director or IO ensure that a thorough investigation is conducted, and if the allegation is determined valid, that corrective action is taken to prevent additional occurrences. In the event that the allegation is regarding the IO, the matter is referred to the Vice Chancellor for investigation and any necessary action.

### 5 Human Subject Research Determination

The responsibility for initial determination whether an activity constitutes human subject research rests with the investigator. The investigator should make this determination based on the definitions of “human subject” and “research” in Section 1.3. For guidance on whether an activity constitutes human subjects research, investigators should refer to the Not Human Subjects Research Application Form. Responsibility for the correct determination belongs to the Investigator and the Investigator is held responsible if the determination is not correct. Investigators may request confirmation that an activity does not constitute human subject research from the IRB Office by submitting a description of the project via Rapport. The
information should include a sufficient description of the activity and the rationale for the investigator’s initial determination.

Determinations whether an activity constitutes human research is made according to the definitions in Section 1.3 using the Not Human Subjects Research Application Form. Determinations regarding activities that are either clearly human research or clearly not human research, based on the Form, may be made by the IRB Office Director, Associate Director or experienced Human Subjects Research Analysts. As needed, the IRB Chair, may make the determination or refer the matter to the full IRB.

Documentation of determinations made through the IRB are recorded and maintained in Rapport or in an internal database.

6 Exempt Studies

All research using human participants must be reviewed prior to initiation. While certain categories of human research are exempt from the requirements of 45 CFR 46, exempt research is subject to review for determination of exemption status. At Dartmouth, exemptions are reviewed and granted by the IRB Associate Director or Human Subject Research Analysts.

Individuals involved in making the determination of an IRB exempt status of a proposed research project cannot be involved in the proposed research or have any apparent conflict of interest.

While exempt studies are exempt from the requirements of the Common Rule [45 CFR 46] (i.e., IRB approval and consent are not required), they do require a determination of exemption status and are not exempt from ethical considerations, such as honoring the principles described in the Belmont Report. The individual/s making the determination of exemption determines whether to require additional protections for research participants in keeping with ethical principles (e.g., requiring disclosure/consent, etc.).

6.1 Limitations on Exemptions

Children: The exemption for research involving survey or interview procedures or observations of public behavior (#2) does NOT apply to research in children, except for research involving observations of public behavior when the investigator does not participate in the activities being observed.

Prisoners: Exemptions do NOT apply. IRB review is required.

6.2 Categories of Exempt Research

With the above-referenced limitations, research activities not regulated by the FDA (See Section 6.3 for FDA Exemptions) in which the only involvement of human participants is
determined to be in one or more of the following categories are exempt from IRB the requirements of 45 CFR 46:

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

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

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:
   (i) the human subjects are elected or appointed public officials or candidates for public office; or
   (ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information is 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:
   (i) Public benefit or service programs;
   (ii) Procedures for obtaining benefits or services under those programs;
   (iii) Possible changes in or alternatives to those programs or procedures; or
   (iv) Possible changes in methods or levels of payment for benefits or services under those programs.
The program under study must deliver a public benefit (e.g., financial or medical benefits as provided under the Social Security Act) or service (e.g., social, supportive, or nutrition services as provided under the Older Americans Act).

The research demonstration project must be conducted pursuant to specific federal statutory authority, there must be no statutory requirements of IRB 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 federal funding agency.

6. Taste and food quality evaluation and consumer acceptance studies,

   (i) If wholesome foods without additives are consumed; or

   (ii) If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

6.3 FDA Exemptions

The following categories of clinical investigations are exempt from the requirements for prior IRB review and approval:

1. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article is subject to IRB review. [21 CFR 56.104(c)]
   
   Note: See Section 13.2 for detailed discussion of this exemption.

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)]

6.4 Procedures for Exemption Determination

In order to obtain an exemption determination, investigators must submit:

1. A completed application to the IRB;
2. All recruitment materials (e.g., letter of invitation, recruitment script, flyer);
3. Consent form/disclosure/information sheet (when appropriate);
4. All surveys, questionnaires, instruments;
5. If federally sponsored/funded, one copy of the grant application(s) and/or contract; and
6. Verification of current human research protection training for all members of the research team as maintained in the IRB Office database.
The IRB reviewer reviews all requests for exemptions and determines whether the request meets the definition of research involving human participants and, if it does, determines whether the proposed research is eligible for exemption. The reviewer determines whether to require additional protections for research participants, in keeping with the guidelines of the Belmont Report.

If there are interactions with participants, the reviewer should determine whether there should be a consent process that will disclose such information as:

- That the activity involves research.
- A description of the procedures.
- That participation is voluntary.
- Name and contact information for the researcher.

The reviewer indicates whether the request for exemption is approved or denied, and if approved, the rationale for the determination and category/s under which it is permitted. The application, review and determination letter are recorded and maintained in the same manner and for the same length of time as other IRB review documentation. Once exemption review is completed, IRB staff sends written notification of the results of the review to the investigator.

Investigators are required to report any proposed modifications to the research that may change the exemption status prior to initiating the change. The reviewer determines if the modified study continues to qualify for exemption.

7 IRB Review Process

The IRB reviews and ensures that Dartmouth research involving human participants meets all required ethical and regulatory criteria for initial and continuing review and any modifications of approved research. The IRB may conduct its review using the following review methods:

- Expedited Review
- Review by Convened IRB

The following describe the procedures required for the review of research by the on-site IRB. (See Section 9 for a description of the procedures for review of research by an External IRB.)

7.1 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.

**Minor Change:** For research reviewed by the convened IRB, a minor change is one which, in the judgment of the IRB reviewer, makes no substantial alteration in:
1. The acceptability of the risk-to-benefit analysis or increases the level of risks to participants;
2. The research design or methods (for example, adding procedures that are not eligible for expedited review (See Section 7.2.2) are considered more than a minor change);
3. The number of participants to be enrolled in the research locally;
4. The qualifications of the research team;
5. The facilities available to support safe conduct of the research;
6. Any other factor which would warrant review of the proposed changes by the convened IRB.

**Quorum:** A quorum of the IRB consists of a majority (more than half) of the voting membership, including at least one member whose primary concern is in a non-scientific area. When research involving an investigational drug is on the agenda for review, a physician is required for quorum.

**Suspension of IRB approval:** Suspension of IRB approval is a directive of the IRB to temporarily stop some or all previously approved research activities. Investigators must continue to provide reports on adverse events and unanticipated problems to both the IRB and sponsors just as if there had never been a suspension (i.e., all events that need to be reported during a study need to continue to be reported during the suspension period). If a suspension is lifted and IRB approval of the suspended research study has expired, a continuing review is required before the study may resume.

**Termination of IRB approval:** Termination of IRB approval is a directive of the convened IRB to permanently stop all activities in an IRB approved research study. Terminated research studies are closed and no longer require continuing review.

7.2 Expedited Review

An IRB may use the expedited review procedure to review:

1. Proposed research in which all human subjects activities appear on the list of categories and is no more than minimal risk.
2. Minor changes in previously approved research by the convened IRB during the period (of one year or less) for which approval is authorized. Note: review of minor changes does not alter the end-date of study approval.

The standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--used by the IRB.

7.2.1 Categories of Research Eligible for Expedited Review

Dartmouth applies the categories of research eligible for expedited review, which were published in the Federal Register notice 63 FR 60364-60367, November 9, 1998 for federally funded research.
The activities listed below should not be deemed to be of 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 participants.

The categories in this list apply regardless of the age of participants, except as noted in category 2.

The expedited review procedure may not be used where identification of participants and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to a participant’s financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections are 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 participants.

**Research Categories one (1) through seven (7) may be used for both initial and continuing IRB 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, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
   - (b) from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week. (Note: Children are defined 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.

3. Prospective collection of biological specimens for research purposes by noninvasive means.
Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing 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; (k) vaginal swabs that do not go beyond the cervical os; rectal swabs that do not go beyond the rectum; and nasal swabs that do not go beyond the nares.

(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. (Note: 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 nonresearch 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)(2) and b(3). This listing refers only to research that is not exempt.) 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.)

Categories 8 and 9 apply only to continuing review.

(8) Continuing review of research previously approved by the convened IRB as follows:

(a) Where (i) the research at Dartmouth 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 (Note: “Long-term follow-up” includes research interactions that involve no more than minimal risk to subjects (e.g., quality of life surveys); and collection of follow-up data from procedures or interventions that would have been done as part of routine clinical practice to monitor a subject for disease progression or recurrence, regardless of whether the procedures or interventions are described in the research study, but not interventions that would not have been performed for clinical purposes, even if the research interventions involve no more than minimal risk.); or

(b) Where no subjects have ever been enrolled at Dartmouth and no additional risks have been identified (Note: “no additional risks have been identified” means that neither the investigator nor the IRB has identified any additional risks from any institution engaged in the research project or from any other relevant source since the IRB’s most recent prior review.); or

(c) Where the remaining research activities at Dartmouth are limited to data analysis. (Note: Simply maintaining individually identifiable private information without using, studying, or analyzing such information is not human subject research and thus does not require continuing review.

(9) Continuing review of research previously approved by the IRB at a convened meeting that meets the following conditions:

- The research is not conducted under an investigational new drug application (IND) or an investigational device exemption (IDE);
- Expedited review categories (2) through (8) do not apply to the research;
- The IRB has determined and documented at a convened meeting that the research, or the remaining research activity involving human subjects, involves no greater than minimal risk to the subjects; and
- No additional risks of the research have been identified. (Note: “no additional risks have been identified” means that neither the investigator nor the IRB has identified any additional risks from any institution engaged in the research project or from any other relevant source since the IRB’s most recent prior review.)
7.2.2 Expedited Review Procedures

Under an expedited review procedure, the review may be carried out by the IRB Chair, or by one or more reviewers designated by the Chair from among members of the IRB. IRB members who serve as designees to the IRB Chair for expedited review are matched as closely as possible with their field of expertise and/or advocacy capacity, as appropriate to the study.

If the Chair is not able to conduct an expedited review, an experienced member will conduct the expedited review. The reviewer(s) will have qualifications, experience and knowledge in the type of research to be reviewed and be knowledgeable of the requirements to approve research under expedited review. IRB members with a conflict of interest in the research (See Section 21.2) will not be selected.

When reviewing research under an expedited review procedure, the IRB Chair, or designated IRB member(s), receives and reviews all documentation submitted. This requirement applies to all categories of submissions including initial reviews, continuing reviews, and modifications. The reviewer determines and documents the regulatory criteria allowing use of the expedited review procedure in the IRB’s electronic system. If the research does not meet the criteria for expedited review, the reviewer indicates that the research requires review by the convened IRB and the research study is placed on the next available IRB meeting agenda.

If the research meets the criteria for expedited review, the reviewer follows the Review Procedures described in Sections 7.2 and 7.4 and may exercise all of the authorities of the IRB except that the reviewer may not disapprove the research. A research activity may be disapproved only after review by the convened IRB (See Section 7.3).

The Reviewer selects approve, require revisions or refer to the convened IRB for review on the Review screen in the IRB’s electronic system and returns it to the IRB Office. If additional information is requested, the investigator receives an email notification and a task in the IRB electronic system that identifies the information being requested. If the reviewer selects approve, the reviewer documents that the research meets the regulatory criteria for approval.

For non-federally funded research meeting the requirements for an expedited review, the IRB may grant a renewal time frame of two years. The two year renewal time frame may be repeated as long as the study is eligible. The IRB may approve continuing review of a project up to 30 days prior to the expiration date while maintaining the anniversary date of the expiration.

7.2.3 Informing the IRB

Any IRB member can click on a link within the Rapport workspace to review any study which has been reviewed via the expedited process or may request to review a hard copy of any study by contacting the IRB Office.
7.3 Convened IRB Meetings

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

7.3.1 IRB Meeting Schedule

IRBs A, C, and D meet on a regular basis throughout the year (usually once per month). The schedule for IRB meetings is posted on the IRB website, https://www.umc.edu/Administration/Business_Services/Human_Research_Office/IRB_Meeting_Dates_and_Deadlines.aspx. but may vary due to holidays or lack of quorum. Special meetings may be called at any time by the IRB Chair or IRB Director.

7.3.2 Pre-Review

The IRB Office staff conducts a pre-review of all submissions for determination of completeness and accuracy. Only complete submissions are placed on the IRB meeting agenda for review. Depending upon timing of the submission, the investigator is informed either through the IRB electronic submission system, by e-mail, phone or in person of missing materials and the necessary date of receipt for inclusion on the agenda. If an investigator is submitting for the first time or is not well-versed in the submission procedures, consultations can be arranged with IRB staff.

7.3.3 Reviewers

After it has been determined that the submission is complete, the IRB Analyst, with the assistance of the IRB Chair as needed, assigns submissions for review, paying close attention to the subject matter of the research, the potential reviewer’s area/s of expertise and representation or advocacy capacity for any vulnerable populations involved in the research. Two reviewers are assigned to each Initial Review, and one reviewer is assigned to each Continuing Review and Amendment. A reviewer may be assigned several submissions or other items for review, such as minutes and continuing education. When the IRB is presented with a research study that may be outside of the knowledge base or representative capacity of the IRB members, an outside consultant is sought (See Section 4.5). Research studies for which appropriate expertise cannot be obtained for a given meeting are deferred to another meeting when appropriate expertise is available.

The named reviewer(s) are responsible for:

1. Having a thorough knowledge of all of the details of the proposed research;
2. Performing an in-depth review of the proposed research;
3. Beginning the discussion of the proposed research at the convened meeting, by summarizing the proposed research and leading the IRB through the regulatory criteria for approval (See Section 7.4).

4. Making suggestions for changes to the proposed research, where applicable.

5. Performing an in-depth review of the proposed research, including review of any relevant grant applications

All IRB members receive and are expected to review all studies, not just those to which they are assigned as a reviewer.

When there is sufficient advance notice that a reviewer will be absent from the meeting, a new reviewer is assigned, provided that the new reviewer will have sufficient time to review the materials in advance of the meeting. An absent reviewer can submit written comments for presentation at the convened meeting, but any recommendation does not count as a vote.

7.3.4 Materials received by the IRB

For inclusion on an IRB meeting agenda, in general, required materials must be complete and will then be added to the next available agenda. The meeting agenda is prepared by the IRB Analyst, in consultation with the IRB Office Director, Associate Director or IRB Chair, as needed. All IRB members receive the meeting agenda, which includes a list of research approved under expedited review procedures since the last meeting, applicable administrative items, continuing education materials and research submission materials no later than 5 days before the scheduled meeting to allow sufficient time for the review process.

All IRB members have access to all materials submitted for all studies on the agenda, which include the following, as applicable:

- The complete Protocol;
- The IRB Study Application Forms (as applicable to the particular study);
- Proposed Consent / Parental Permission / Assent Form(s); and
- Proposed recruitment materials, including advertisements intended to be seen or heard by potential study participants;
- Grant application(s);
- Investigator Brochure(s)

Additionally, for DHHS-supported multicenter clinical trials, the primary reviewer should receive and review a copy of the DHHS-approved sample informed consent document(s) (when one exists) and the complete DHHS-approved protocol/research plan (when one exists).

If an IRB member requires additional information to complete the review, he/she may contact the investigator directly or may contact the IRB Office to make the request of the investigator.
7.3.5 Quorum

A quorum of the IRB consists of a majority (more than half) of the voting membership, including at least one member whose primary concern is in a non-scientific area. At IRB meetings, a quorum must be established and maintained for the deliberation and vote on all matters requiring a vote.

The IRB Chair, with the assistance of the IRB staff, confirms that quorum is present before calling the meeting to order. The IRB Chair, with the assistance of the IRB staff, is responsible for ensuring that the IRB meeting remains appropriately convened. The IRB Staff notifies the IRB Chair when a quorum is not present. If quorum is not maintained, either by losing a majority of the members, losing all non-scientific members or another required member, the IRB will not take further action or vote on regulatory determinations until quorum is restored even if half of the members are still present.

Attendance and vote count are documented by the IRB Staff for each study on the agenda and within the review area of the IRB’s electronic system.

It is expected that at least one unaffiliated member and at least one member who represents the general perspective of participants (one individual can serve in both capacities) is present at all IRB meetings. The IRB may, on occasion, meet without this representation; however, this is the exception. No more than 1/3 of the IRB meetings may take place without an unaffiliated member present.

If the IRB regularly reviews research that involves a vulnerable category of participants, such as children, prisoners, pregnant women, or persons with impaired decision-making capacity, one or more individuals (e.g., IRB members, alternate members, or consultants) who are knowledgeable about and experienced with that population should be present during the review of the research.

When the IRB is presented with a research study which may be outside of the knowledge base or representative capacity of the IRB members, an outside consultant will be sought. Research studies for which appropriate expertise cannot be obtained for a given meeting will be deferred to another meeting when appropriate expertise is available.

IRB members are considered present and participating at a convened IRB meeting when either physically present or participating through electronic means (e.g., teleconferencing or video conferencing) that permits them to listen to and speak during IRB deliberations and voting. Whether or not physically present, the IRB member must have received all pertinent materials 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 IRB members but may not be counted as votes or to satisfy the quorum for convened meetings.
7.3.6  Meeting Procedures

Once it has been determined that a quorum is in place the IRB Chair calls the meeting to order. The agenda reminds IRB members to recuse themselves from any vote when they have a conflict.

The IRB reviews all submissions for initial and continuing review, and requests for revisions that are not otherwise eligible or appropriate for review by expedited procedures. The reviewers present an overview of the research and assist the Chair in leading the IRB through a discussion of the regulatory criteria for approval, which is available during the meeting, either projected onto a screen or in hard copy, to help guide the discussion. In order for the research to be approved, it must receive the approval of a majority of those voting members present at the meeting.

Electronic access to protocols is available to all members at all times. The majority of members bring a laptop to meetings and are projected onto a screen during the meeting. Each member receives a laminated list of the Criteria for IRB Approval of Research at the beginning of each meeting. In addition, when the Committee reviews research involving Children, a laminated guidance sheet describing review requirements is distributed.

The IRB Analyst and IRB Office Director take notes of the proceedings and the IRB Analyst is responsible for preparing the meeting minutes.

7.3.7  Guests

Investigators and research staff may be invited to the IRB meeting, at the discretion of the IRB, to make a brief presentation or to answer questions about proposed or ongoing research. The investigator/research staff may not be present for the deliberations or vote on the research.

The IRB Office Director and staff regularly attend IRB meetings and may participate in the IRB discussion and deliberations.

Other guests may be permitted to attend IRB meetings at the discretion of the IRB Chair and the IRB Office staff. Such guests are asked to sign a confidentiality agreement, do not participate in discussion unless requested by the IRB, and they are not allowed to vote.

7.4  Criteria for IRB Approval of Research

In order for the IRB to approve human subjects research, either through expedited review or by the convened IRB, it must determine that the following requirements are satisfied. These criteria apply to all categories of IRB reviews including initial reviews, continuing reviews, and amendments of previously approved research.

(1) 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 purposes.
(2) 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 IRB 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 IRB 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.

(3) Selection of subjects is equitable. In making this assessment the IRB 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 disable persons, or economically or educationally disadvantaged persons.

(4) 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 the Federal Regulations [45 CFR 46.116].

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by the Federal Regulations [45 CFR 46.117].

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

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

(8) 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.

### 7.4.1 Risk/Benefit Assessment

The goal of the assessment is to ensure that the risks to research participants posed by participation in the research are justified by the anticipated benefits to participants or society. The IRB must:

- Judge whether the anticipated benefit, either of new knowledge or of improved health or other direct benefit for the research participant, justifies asking any person to undertake the risks; and
- Disapprove research in which the risks are judged unreasonable in relation to the anticipated benefits.

The assessment of the risks and benefits of proposed research involves a series of steps:
1. **Identify the risks** associated with the research, as distinguished from the risks of activities, diagnostic tests, treatments, or therapies participants would receive even if not participating in research;

2. **Determine whether the risks are minimized** to the extent possible by evaluating the necessity of procedures that impart risk and whether the data could be gained by procedures that are already being performed for other purposes or by alternative procedures that impart less risk;

3. **Identify the anticipated benefits** to be derived from the research, both direct benefits to participants and possible benefits to society, science and others;

4. **Determine whether the risks are reasonable in relation to the benefits**, if any, and assess the importance of the knowledge to be gained;

In addition to evaluation of the risks in the research, the IRB determines, based on the materials submitted by the investigator, that research studies have the resources necessary to protect participants, such as adequate time for the researchers to conduct and complete the research, adequate number of qualified staff, adequate facilities, access to a population that will allow recruitment of the necessary number of participants, availability of medical or psychosocial resources that participants might need as a consequence of the research.

The IRB should not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks and benefits that fall within the purview of its responsibility.

### 7.4.1.1 Scientific or Scholarly Review

In order to assess the risks and benefits of the proposed research, the IRB must determine that:

- The research uses procedures consistent with sound research design; and
- The research design is sound enough to reasonably expect the research to answer its proposed question.

In making this determination, the IRB may draw on its own knowledge and expertise, or the IRB may draw on the knowledge and expertise of others, such as reviews by a funding agency, or departmental review. Scientific or scholarly review may be delegated to a departmental or other appropriate review committee. When scientific or scholarly review is conducted by an individual or entity external to the IRB, documentation that the above items were considered must be provided to the IRB for review and consideration. External scientific or scholarly review is documented and provided to the IRB through its electronic system.

### 7.4.2 Equitable Selection of Participants

The IRB determines by reviewing the application, protocol/research plan and other materials that the selection of subjects is equitable with respect to gender, age, class, etc. The IRB will not approve a study that does not provide adequately for the equitable selection of research participants or does not provide an appropriate scientific and ethical justification for excluding
classes of persons who might benefit from the research. In making this determination, the IRB evaluates:

- The purposes of the research;
- The setting in which the research occurs;
- Scientific and ethical justification for including vulnerable populations such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons;
- The scientific and ethical justification for excluding classes of persons who might benefit from the research; and
- The inclusion/exclusion criteria, and the procedures/materials intended for use for the identification and recruitment of potential participants.

At the time of continuing review the IRB verifies that there have been no unacceptable changes in the participant selection criteria that was originally set forth at the time of the initial IRB review and approval.

7.4.2.1 Recruitment of Participants

The investigator provides the IRB with a plan for recruitment of all potential participants. All recruiting materials are submitted to the IRB, including advertisements, flyers, scripts, information sheets and brochures. The IRB ensures, as part of its review, that the recruitment plan and materials appropriately protect the rights and welfare of prospective participants (e.g., do not present undue influence). See Section 7.5.10 for a discussion of IRB review of advertisements and Section 7.5.11 for a discussion of IRB review of payments.

7.4.3 Informed Consent

The IRB ensures that informed consent will be sought from each prospective participant or the participant’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 IRB 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. The IRB has the authority to issue waivers or alterations to the consent requirement, process, or documentation. The IRB ensures, as part of its review, that the information in the consent document and process is consistent with the research plan, and, when applicable, the HIPAA authorization. See Section 11 for detailed policies on informed consent.

7.4.4 Data and Safety Monitoring

For research that is more than minimal risk, the investigator should submit a data and safety monitoring plan as applicable to the nature of the research. The initial plan submitted to the IRB should describe the procedures for safety monitoring, reporting of unanticipated problems
involving risks to participants or others, descriptions of interim safety reviews and the procedures planned for transmitting the monitoring results to the IRB.

The IRB reviews the safety monitoring plan and determines if it makes adequate provision for monitoring the reactions of participants and the collection of data to ensure the safety of participants and address problems that may arise over the course of the study. If a plan is not submitted, the IRB determines whether or not a plan is required, and, depending on the circumstances, what the plan should include. The overall elements of the monitoring plan may vary depending on the potential risks, complexity, and nature of the research study.

The factors the IRB considers in determining whether the safety monitoring plan is adequate for the research include:

1. Monitoring is commensurate with the nature, complexity, size and risk involved;
2. Monitoring is timely; frequency commensurate with risk; and conclusions reported to the IRB;
3. For low risk studies, close monitoring by the study investigator or an independent individual may be adequate and appropriate, with prompt reporting of problems to the IRB, sponsor and regulatory bodies, as applicable;
4. The Data and Safety Monitoring plan should specify:
   • The entity or person(s) who will perform the monitoring, and the independence or affiliation that the entity or person(s) has with the sponsor or investigator;
   • The safety information that will be collected and monitored, including serious adverse events and unanticipated problems;
   • The frequency of review of safety data;
   • The procedure for analysis and interpretation of the data;
   • The procedure for review of scientific literature and data from other sources that may inform the safety or conduct of the study;
   • The conditions that will trigger a suspension or termination of the research (i.e., stopping rules), if applicable;
   • The procedure for reporting to the IRB, including a summary description of what information, or type of information, will be provided.
5. For a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC), the plan should describe:
   • The composition of the board or committee. Generally, a DSMB should be composed of experts in all scientific disciplines needed to interpret the data and ensure participant safety. Clinical trial experts, biostatisticians, bioethicists, and clinicians knowledgeable about the disease/condition and treatment under study should be part of the monitoring group or be available if warranted.
• Frequency and content of meeting reports;

• The frequency and character of monitoring meetings (e.g., open or closed, public or private);

• The Charter should be provided, when one exists;

For multi-site studies, blinded studies or studies that involve vulnerable populations or employ high-risk interventions, the DSMB or DMC should be established by the study sponsor. For some studies the National Institutes of Health (NIH) requires a DSMB. The IRB has the authority to require a DSMB or DMC as a condition for approval of research, where it determines that such monitoring is needed. When DSMBs or DMCs are used, during continuing review the IRB may rely on a current statement, or the most recent report, from the DSMB or DMC which indicates that it has and will continue to review study-wide adverse events, study wide interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB.

7.4.5 Privacy and Confidentiality

The IRB determines if adequate procedures are in place to protect the privacy of participants and to maintain the confidentiality of the data.

7.4.5.1 Definitions

Privacy: Having control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others. It is the state or condition of being free from unauthorized intrusion, being observed or disturbed by other people.

Confidentiality: Methods used to ensure that information obtained by investigators about participants is not improperly divulged.

Private information: Information that 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).

Sensitive Information: Data or information, on any storage media or in any form or format, which requires protection due to the risk of harm that could result from inadvertent or deliberate disclosure, unauthorized access, misuse, alteration, or loss or destruction of the information (e.g., could reasonably place the participant at risk of criminal or civil liability or be damaging to the participant’s financial standing, employability, or reputation).

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

7.4.5.2 Privacy

The IRB must determine whether the activities in the research appropriately protect the privacy of potential and actual participants. In order to make that determination, the IRB must obtain information regarding how the investigators plan to access participants and/or participants’
private, identifiable information and the participants’ expectations of privacy in the situation. Investigators must have appropriate authorization to access participants or the participants’ information.

In developing strategies for the protection of participants’ privacy, consideration is given to:

1. Methods used to identify and contact potential participants;
2. Settings in which an individual will be interacting with an investigator;
3. Appropriateness of all personnel present for research activities;
4. Methods used to obtain information about participants, and the nature of the requested information including minimizing the information obtained to achieve the aims of the research;
5. Information that is obtained about individuals other than the “target subjects,” (e.g., a participant provides information about a family member for a survey) and whether such individuals meet the regulatory definition of “human subject”.

7.4.5.3 Confidentiality

The IRB must determine if appropriate protections are in place to minimize the likelihood that information about participants will be inappropriately divulged. Safeguards designed to protect confidentiality should be commensurate with the potential of harm from unauthorized, inappropriate or unintentional disclosure.

At the time of initial review, continuing review and with any requests for revisions, the IRB assesses whether there are adequate provisions to protect data confidentiality. The IRB does this through the evaluation of the methods used to obtain, record, share, and store information about individuals who may be recruited to participate in studies and about individuals who agree to participate. The investigator provides the IRB with the plan to protect the confidentiality of research data and sensitive information, including information security procedures (use, maintenance, storage and transmission) and the protection of paper documents, other physical media (e.g., audio or videotapes). The IRB reviews all information received and determine whether or not the confidentiality of research data is sufficiently protected. In some cases, the IRB may also require that a Certificate of Confidentiality be obtained to additionally protect research data (See Section 25.4).

In reviewing confidentiality protections, the IRB considers whether or not the data or other information accessed or gathered for research purposes is sensitive and the nature, probability, and magnitude of harms that would be likely to result from a disclosure of collected information outside the research. The IRB considers regulations and organizational policies and evaluate the effectiveness of proposed de-identification techniques, coding systems, encryption methods, methods of transmission, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections.

Research regulated by the FDA that involves the use of electronic data collection/storage systems must also comply with the requirements of 21 CFR Part 11 as applicable.
7.4.6 **Vulnerable Populations**

Certain individuals, by nature of age or mental, physical, economic, educational, or other situation, may be more vulnerable to coercion or undue influence than others. At the time of initial review the IRB considers the scientific and ethical reasons for including vulnerable participants in research. The IRB may determine and require that, when appropriate, additional safeguards be put into place for vulnerable participants, such as those without decision-making capacity.

For an extensive discussion about the IRB’s review and approval process for individual populations of vulnerable participants, see Section 12.

7.5 **Additional Considerations**

7.5.1 **Determination of Risk**

At the time of initial and continuing review, the IRB makes a determination regarding the risks associated with the research. Risks associated with the research are classified as either “minimal” or “greater than minimal”, with additional classifications as required by the regulatory subparts or FDA regulations. Risk determinations may vary over the life of a research plan, depending on the procedures and risks that participants are exposed to as the research progresses. The level of risk associated with the research influences eligibility for expedited review. The determination of risk level, whether by the convened IRB or the expedited reviewer, are documented within the review screen(s) and reflected on the overall protocol information in the IRB’s electronic system.

7.5.2 **Period of Approval**

At the time of initial review and at continuing review, the IRB makes a determination regarding the frequency of review of the study. All studies are reviewed by the IRB at intervals appropriate to the degree of risk. Federally-funded studies continuing review is no less than once per year. For non-federally funded research meeting the requirements for an expedited review, the IRB may grant a renewal time frame of two years. In some circumstances, a shorter review interval (e.g., semi-annually, quarterly, or after accrual of a specific number of participants) may be required (see below). For all studies (whether convened or expedited review) the IRB’s electronic system and meeting minutes reflect the approval start and end date and the review frequency is documented in the IRB’s electronic system.

7.5.3 **Review More Often Than Annually**

The following factors are considered when determining which studies require review more frequently than once per year:

1. The probability and magnitude of anticipated risks to participants;
2. The likely medical/psychological/social/legal/educational condition of the proposed participants;
3. The qualifications of the investigator and other members of the research team;
4. The specific experience of the investigator and other members of the research team in conducting similar research;
5. The nature and frequency of adverse events observed in similar research;
6. The novelty of the research, which may make unanticipated events/problems more likely;
7. The involvement of vulnerable populations likely to be subject to undue influence or coercion (e.g., terminally ill);
8. A history of serious or continuing non-compliance on the part of the investigator;
9. Any other factors that the IRB deems relevant.

In specifying an approval period of less than one year, the IRB may define the period with either a time interval or a maximum number of participants either studied or enrolled. If a maximum number of participants studied or enrolled is used to define the approval period, the number of participants studied or enrolled determines the approval period only when that number of participants is studied or enrolled in less than one year. If an approval period of less than one year is specified by the IRB, the reason for more frequent review is documented in the electronic protocol record, meeting minutes or the expedited reviewer’s review comments.

7.5.4 Independent Verification That No Material Changes Have Occurred

The IRB recognizes that protecting the rights and welfare of study participants sometimes requires that the IRB use sources other than the investigator to independently verify that no material changes occurred during the IRB-designated approval period.

The IRB determines the need for verification from outside sources on a case-by-case basis. When determining which studies require verification from outside sources, the IRB considers all factors, including, but not limited to:

1. The probability and magnitude of anticipated risks to participants;
2. The likely medical/psychological/social/legal/educational condition of the proposed participants;
3. The probable nature and frequency of changes that may ordinarily be expected in the type of research proposed;
4. Concern about possible material changes occurring without IRB approval have been raised based on information provided in continuing review reports or from other sources;
5. Investigators who have previously failed to comply with federal regulations and/or the requirements or determinations of the IRB;
6. Research without a routine monitoring plan;

In making a determination about independent verification, the IRB may prospectively require that such verification take place at predetermined intervals during the approval period, or may require such verification at the time of continuing review, review of amendment requests and/or report of an unanticipated problem.

If the IRB finds that any material changes have occurred without IRB review and approval, the IRB decides the corrective action to be taken (See Section 16 on Non-compliance).

7.5.5 Consent Monitoring

In reviewing the adequacy of informed consent procedures for proposed research, the IRB may determine that monitoring of the consent process by an impartial observer (e.g., consent monitor) is required in order to reduce the possibility of coercion and undue influence, ensure that the approved consent process is being followed, and/or ensure that participants are truly giving informed consent.

Such monitoring may be particularly warranted for:

1. High risk studies;
2. Studies that involve particularly complicated procedures or interventions;
3. Studies involving highly vulnerable populations (e.g., ICU patients, children who are wards);
4. Studies involving study staff with minimal experience in obtaining consent; or
5. Other situations when the IRB has concerns that the consent process may not be/is not being conducted appropriately (e.g., prior investigator non-compliance, etc.).

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

If the IRB determines that consent monitoring is required, the IRB Chair and the IRB Office Director develop a proposed monitoring plan and submit it to the IRB for approval. The consent monitoring may be conducted by IRB staff, IRB members or another party, either affiliated or not with Dartmouth. The investigator is notified of the IRB’s determination and the reasons for the determination. Arrangements are made with the investigator for the monitoring of the consent process, typically for a specified number of participants. When observing the consent process, the monitor determines:

- Whether the informed consent process was appropriately conducted and documented;
- Whether the participant had sufficient time to consider study participation;
- Whether the consent process involved coercion or undue influence;
• Whether the information was accurate and conveyed in understandable language; and
• Whether the participant appeared to understand the information and gave voluntary consent.

Following the monitoring, a report of the findings is submitted to the IRB, which determines the appropriate action, if any, to be taken.

7.5.6 Investigator Qualifications

The HRPP may review credentials, curriculum vitae, resumes, or other relevant materials to determine whether investigators and members of the research team are appropriately qualified to conduct the research. In general, the HRPP relies upon Dartmouth Chair and internal processes (e.g., credentialing and departmental review) to inform this determination.

7.5.7 Investigator Significant Financial Interest / Conflicts of Interest (COI)

The IRB research application asks a question related to significant financial interests (SFI) in order to identify potential COI of the investigator or research team member. In addition, the Office of Sponsored Research and Research Compliance Office maintain annual disclosures from researchers. As part of the review process, the Conflict of Interest Committee (COIC) and IRB make a final determination as to whether any SFI constitutes a conflict of interest whereby the design, conduct, or reporting of the research could be impacted. The IRB has final authority to determine whether the determination and the management plan, if any, allow the study to be approved. (See Section 21 for a more detailed discussion of COI.)

7.5.8 Institutional Conflicts of Interest

The Conflict of Interest Committee (COIC) including membership of IRB members has final authority to determine whether the Institutional Conflict, the Financial Interest, and the management plan, if any, allow the study to be approved. See Section 21.3 for a more detailed discussion of Institutional COI.

7.5.9 Significant New Findings

During the course of research, significant new knowledge or findings about the research, the test article, and/or the condition under study may develop. The investigator must report any significant new findings to the IRB and the IRB reviews them with regard to the impact on the participants’ rights and welfare. Because the new knowledge or findings may affect the risks or benefits to participants or participants' willingness to continue in the research, the IRB may require, during the ongoing review process, that the investigator contact the currently enrolled participants to inform them of the new information. The IRB communicates this requirement to the investigator. If the study is still enrolling participants, the consent document should be updated. IRB may require that the currently enrolled participants be re-consented or otherwise
provided with the new information. The IRB may also require that former participants be provided with the new information, e.g., if it impacts their rights or welfare.

7.5.10 Advertisement and Recruitment Materials

The IRB must review and approve any and all advertisements prior to posting and/or distribution for studies that are conducted under the purview of Dartmouth. The material the IRB reviews includes, but is not limited to:

1. The information contained in the advertisement;
2. The mode/method of its communication;
3. The final copy of printed advertisements; and
4. The proposed script and final audio/video taped advertisements.

This information is submitted to the IRB with the initial application or, if recruitment is proposed after study approval, as an amendment.

The IRB reviews the material to assure that the material is accurate and is not coercive or unduly optimistic, creating undue influence on the participant, including but not limited to:

1. Statements implying a certainty of favorable outcome or other benefits beyond what was outlined in the consent document and the research plan;
2. Claims, either explicitly or implicitly, that the test article (drug, biologic or device) is safe or effective for the purpose(s) under investigation; and
3. Claims, either explicitly or implicitly, that the test article is equivalent or superior to any other drug, biologic or device.

The IRB generally does not allow the following phrases/language in the material:

1. Where an experimental drug, device or treatment is part of the study, terms like “new treatment”, “new medication” or “new drug” are not allowed and the test article must be referred to as experimental.
2. Specific payment amounts may not be emphasized.
3. Exculpatory language.
4. Promise of free medical treatment
5. Offers for a coupon good for a discount on the purchase price of an investigational product once it has been approved for marketing.

Recruitment materials should be limited to the information prospective participants need to determine possible eligibility and interest. The following items must be included:

1. The name and address of the investigator and/or research facility;
2. The condition being studied and/or the purpose of the research;
3. The location of the research and the person or office to contact for further information.
4. A clear statement that that study involves research and not treatment.
When appropriately worded the material may also include:

1. In summary form, the criteria used to determine eligibility for the study;
2. The time or other commitment required;
3. A brief list of potential benefits.

Once approved by the IRB, an advertisement may not be altered or manipulated in any way without prior IRB approval.

Directory listings of research such as ClinicalTrials.Gov are not considered advertisements and do not require IRB review and approval if the listing is limited to the following basic information: title, purpose of the study, research plan summary, basic eligibility criteria, study site location(s), and how to contact the study site for further information.

For recruitment materials, the first contact prospective study participants make is often with a person who follows a script to determine basic eligibility for the specific study. The IRB reviews the procedures to be followed and verifies that they adequately protect the rights and welfare of prospective participants.

**7.5.11 Payment to Research Participants**

Payment to research participants may be an incentive for participation or to reimburse a participant for travel and other out-of-pocket expenses incurred due to participation. However, payment for participation is not considered a research benefit. Regardless of the form of remuneration, investigators must take care to avoid unduly influencing participants. The amount of compensation or reimbursement should be proportional to the time and inconveniences posed by participation in the study.

Investigators who wish to pay research participants must submit to the IRB the amount and schedule of all payments. Investigators must indicate in the IRB application the justification for such payment. Such justification should substantiate that proposed payments are reasonable and commensurate with the expected contributions of the participant and do not constitute (or appear to constitute) undue pressure on the potential participant to volunteer for the research study.

The IRB must review both the amount of payment and the proposed method and timing of disbursement to assure that neither entails problems of coercion or undue influence.

Compensation must be prorated and not be contingent upon the participant completing the entire study. The IRB does not allow payment to be contingent upon completion of the study. Any amount paid as bonus for completion of the entire study may not be so great that it could unduly induce a participant to remain in the study when he/she otherwise would have withdrawn.

The consent form must describe the terms of payment including the amount and schedule of payments and any conditions under which participants will receive partial payment (e.g., if they withdraw from the study before participation is complete) or no payment.
Unless the study is confidential, the clinical trials office requires identifying information to issue checks, cash, or gift certificates to participants. The consent form must inform participants that they will be asked to provide their Social Security Number. For confidential studies, only name and address are required by the accounting office, but the investigator MUST keep an identity key in a secure place.

### 7.5.12 Non-Monetary Gifts and Incentives

Similar to financial incentives, non-monetary gifts or incentives can also present problems of undue influence or coercion that impact a potential participant’s ability to fully and freely consider participation in research.

If participants are provided with non-monetary gifts or tokens of appreciation, such as tote bags, books, toys, or other such materials, the approximate retail value must be described to the IRB, along with a description, photo, or sample product to review.

The IRB reviews all gifts and incentives, being particularly sensitive to the influence of power or authority, whether perceived or actual, over free decision-making. Overt coercion (e.g., threatening loss of credit, or access to services or programs, to which potential participants are otherwise entitled) is never allowed. Regardless of an individual’s choice of participation, it will have no adverse effect on his/her relationship with the organization, its staff or the provision of services in any way (e.g., access to medical care).

Investigators should carefully structure incentives and methods of disbursement so that the incentive may serve as a factor in the decision to participate, but not serve to unduly influence or coerce participation.

### 7.5.13 State and Local Laws

The IRB considers and adheres to all applicable state and local laws in the jurisdictions where the research is taking place. The IRB relies on Counsel for the interpretation and application of New Hampshire law and the laws of any other jurisdiction where the research is being conducted as they apply to participants in human research. The IRB ensures that consent forms are consistent with applicable state and local laws.

### 7.6 Possible IRB Actions

**Approve:** The research, proposed modification to previously approved research, or other item is approved. The IRB has made all of the determinations required for approval (i.e., approval criteria and any applicable special determinations (e.g., waivers, alterations, vulnerable population determinations, etc.)). No further action is needed.

**Modifications Required to Secure Approval (MRSA):** 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, a CPHS Director, an 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.

When the IRB requires conditions or additional information before approval, the conditions or additional information is documented in the electronic review system.

The date of approval is the date the conditions were determined to be met. In the case of modifications, if IRB approval of the research expires before the conditions are reviewed and approved, all research activities must stop until IRB approval is obtained.

After verification, the following is documented in IRB records and written communication to the investigator:

- The date when verification was made that all IRB conditions have been satisfied (i.e., the “effective date of approval”); and
- The date by which continuing review must occur.

**Partial Approval.** The IRB may stipulate that certain components of the research, which the IRB has determined to meet the criteria for approval, may commence or continue while other components of the research that require modification or clarification cannot begin or continue until the outstanding issues are resolved and approved by the convened IRB. For example, the IRB could determine that a study may begin but that children cannot be enrolled until the investigator submits, and the IRB approves, a plan for assent.

**Disapproval:** The concerns of the Committee are substantive in content. The magnitude and number of concerns, questions, or problems are more than minor. A decision to disapprove indicates that the convened Committee will review the response including any revised study documents, prior to approval of the study.
In order to receive approval for a study that has been disapproved:

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

b. Approval of the study is not granted until any modifications made by the investigator satisfy CPHS reviewers.

c. Final approval of the study is communicated to the investigator in writing.

d. The review of the response and revised documents is documented in Rapport.

An expedited reviewer cannot disapprove a study or revisions to a study already approved.

Approval in Principle: Federal regulations, [45CFR46.118], identify circumstances in which a sponsoring agency may require certification of IRB approval as a condition of submitting for or releasing funds but before definitive plans for the involvement of human participants have been developed (e.g., certain training grants or grants in which the procedures involving human participants are dependent on the completion of animal studies or instrument development). In these circumstances, the IRB may grant “approval in principle” without having reviewed the as yet undeveloped procedures or materials. The IRB Chair or designee reviews the available information (i.e., the grant or proposal and any supplemental information provided by the investigator) and, if appropriate, provides certification of IRB approval in principal. The investigator must submit the study for subsequent review and approval by the IRB prior to the involvement of human participants.

7.7 Continuing Review

The IRB conducts a continuing review of ongoing research at intervals that are appropriate to the level of risk for each research plan, but not less than once per year except in the case of non-federally funded research meeting the requirements for an expedited review, the IRB may grant a renewal time frame of two years. The date by which continuing review must occur is recorded in the IRB minutes or other IRB records and communicated in writing to the investigator. Continuing review must occur as long as the research remains active including when the remaining research activities are limited to the analysis of private identifiable information.

7.7.1 Approval Period

At the time of initial review and at continuing review, the IRB makes a determination regarding the frequency of review of the research study. All studies are reviewed by the IRB at intervals appropriate to the degree of risk but no less than once per year except in the case of non-federally funded research meeting the requirements for an expedited review, the IRB may grant a renewal time frame of two years. See Section 7.5.3 for a detailed discussion of Review More Often Than Annually. For a new investigator or an investigator who has recently had a study
suspended by the IRB due to regulatory concerns, an on-site review by a subcommittee or
designee of the IRB might occur or approval might be subject to an audit of study performance
after a few months of enrollment, or after enrollment of the first several participants. The
review frequency is documented in the IRB’s electronic system and the system and meeting
minutes reflect the approval start and end date.
IRB approval ends at midnight on the expiration date of the approval (i.e., the expiration date is
the last day research can be conducted). For a new study reviewed by the IRB, approval
commences on the date that the IRB conducts its final review of the study; that is, the date that
the convened IRB or expedited reviewer approves the research or the date (“effective date”)
that it is verified that the requirements of the IRB have been satisfied following an action of
Revisions Required. The expiration date of the initial approval period, which is the date by
which the first continuing review must occur, may be as late as one year after the effective date
doing initial IRB approval.
The use of the effective date of IRB approval to determine the latest permissible date for
continuing review only applies to the first continuing review. For all subsequent continuing
reviews of a research study, the date the convened IRB or the expedited reviewer conducts
continuing review and approves the study determines the latest permissible date of the next
continuing review. If the IRB performs continuing review within 30 days before the IRB
approval period expires, the IRB may retain the anniversary date as the date by which the
continuing review must occur.
The approval date and approval expiration date are clearly noted on IRB determination letters
and must be strictly adhered to. Investigators should allow sufficient time for development and
review of continuing review submissions.
IRB review of a proposed modification to research does not alter the date by which continuing
review must occur. This is because continuing review is review of the full research project, not
simply a change to it.
The regulations make no provision for any grace period extending the conduct of research
beyond the expiration date of IRB approval. Therefore, continuing review and re-approval of
research must occur by midnight of the date when IRB approval expires.

7.7.2 Continuing Review Process

As a courtesy to investigators, the IRB electronic system sends 3 renewal reminders, 90, 60 and
30 days prior to expiration; however, it is the investigator’s responsibility to ensure that the
continuing review of ongoing research is approved prior to the expiration date. By federal
regulation, no extension to that date can be granted. No changes may be made with the
continuing review submission.

Investigators must respond to items on the Rapport ‘smart form’ and submit the following for
continuing review:

1. The most recent report from the DSMB or Dartmouth-Hitchcock Safety Monitoring and
Accrual Committee (DSMAC) (if applicable);
and

2. The continuing review form.

All information is submitted electronically and IRB members have access to the complete study file at all times.

### 7.7.3 Approval Considerations

In order to re-approve research at the time of continuing review, the IRB must determine that the regulatory criteria for approval continue to be satisfied. Because the research was previously found to satisfy the criteria for approval, the IRB focuses its considerations at the time of continuing review on whether any new information is available that would affect the IRB’s prior determination that the criteria for approval are satisfied. The IRB pays particular attention to four aspects of the research:

1. Risk assessment and monitoring;
2. Adequacy of the informed consent process;
3. Local investigator and organizational issues; and
4. Research progress.

### 7.7.4 Convened Board Review

In conducting continuing review of research not eligible for expedited review, all IRB members are provided with access to all of the materials listed in Section 7.7.2 and are responsible for reviewing the project summary, the current consent document, the progress report, and, if applicable, the data and safety monitoring report, and multi-center study progress reports. The Reviewer is responsible for reviewing the complete materials submitted for continuing review including the complete research plan and is given access to the complete IRB file. At the meeting, the Reviewer assists the Chair in leading the IRB through the discussion of the submission and the regulatory criteria for approval.

Review of currently approved consent documents occurs during the continuing review of research by the IRB. If the Continuing Review contains information that might alter the protocol, study procedures or consent document, for example the identification of new risks, the IRB considers whether changes are needed to the consent document, protocol or study procedures.

### 7.7.5 Expedited Review

In conducting continuing review under expedited procedures, the reviewer receives all of the previously noted materials. The reviewer determines whether the research meets the criteria for continuing review using the expedited procedure, and if so, whether the research continues to meet the regulatory criteria for approval.
If research did not qualify for expedited review at the time of initial review, it does not qualify for expedited review at the time of continuing review, except in limited circumstances described by expedited review categories (8) and (9) (see Expedited Review Categories in Section 7.2.1). It is also possible that research activities that previously qualified for expedited review, have changed or will change, such that expedited IRB review is no longer permitted for continuing review. Additionally, the Committee may opt to review research that is eligible for expedited review at convened meetings for a period of time, for example, the first year, and then assign the study to receive expedited review.

7.7.6 Possible IRB Actions after Continuing Review

At the time of Continuing Review, the Convened IRB or IRB Member(s) conducting expedited review may take any of the following actions (see Section 7.6 for a detailed description of these actions):

1. Approve
2. Modifications Required to Secure Approval (MRSA)

Additionally, the convened IRB may vote to disapprove the study. If an IRB member conducting expedited review believes that the study should be disapproved, it is referred to the convened IRB for review. If the IRB has significant concerns, the IRB may vote to suspend or terminate the research (See Section 8 for a detailed discussion of suspensions and terminations).

If the Continuing Review determination is Modifications Required, the IRB specifies any conditions that must be satisfied before an investigator can continue particular research activities related to those conditions or requirements that must be adhered to until the conditions of approval have been satisfied. For example, if at the time of continuing review, the IRB requires the investigator to change the research protocol to include a specific new procedure for screening prospective participants, the IRB could approve the research with the following condition: research activities involving currently enrolled participants may continue, but no new participants may be enrolled until a designated IRB member reviews a revised protocol and verifies that the protocol includes the new screening procedure. Additionally, the IRB may specify a time period for the condition(s) to be satisfied, as long as the activity with conditions is not begun/restarted until approval is granted.

7.7.7 Lapse in Approval

The regulations permit no grace period or approval extension after approval expires. Research that continues after the approval period has expired is research conducted without IRB approval. If re-approval does not occur before the stated expiration date, all research activities must stop, including recruitment (media advertisements must be withdrawn), enrollment, consent, interventions, interactions, and data collection. This occurs even if the investigator has provided the continuing information before the expiration date. Expiration Notices are sent to Investigators the day following approval expiration. This occurs even if the investigator has
submitted a Continuing Review application. The notice reminds investigators that all research activities must stop.

The lapse of IRB approval due to a failure to complete continuing review and obtain re-approval prior to expiration of the prior approval does not ordinarily constitute a suspension or termination of IRB approval, for federal reporting purposes. Lapses are administratively closed.

If approval expires, while enrollment of new participants cannot occur after the expiration of IRB approval, temporarily continuing participation of already enrolled participants may be necessary or appropriate, for example, when the research interventions hold out the prospect of direct benefit to the participants, or when withholding those interventions or safety monitoring procedures might pose a harm to participants. In these instances, the investigator must notify the IRB, at the earliest opportunity, and submit a request to continue those research activities that are in the best interests of participants. Such a request should specifically list the research activities that should continue, and provide justification, and indicate whether the request applies to all or only certain participants. The IRB Chair or designee reviews the request and provides a determination regarding what activities, if any, may continue during the lapse. Such a determination may include a time limit or other conditions or restrictions. If the IRB decides that already enrolled participants should continue to receive the interventions that were being administered to participants under the research project, data collection (especially safety information) should also continue for such participants.

When there is insufficient time to obtain an IRB determination (e.g., the study regimen includes daily administration of an experimental agent), the investigator may make an initial determination, in consultation with the participants' treating physician, if appropriate. In such cases, the investigator must, as soon as possible, notify the IRB and submit a request for confirmation that the IRB agrees with the determination. The IRB Chair or designee reviews the request and provide a determination. In the event that the IRB does not agree with the investigator's determination, or only agrees in part (e.g., agrees that some but not all of the activities are in the best interests of participants), the IRB notifies the investigator who must then comply with the IRB's requirements or request a re-review of the determination by providing additional justification or information that the IRB may not have considered.

7.8 Amendment of an Approved Protocol

Investigators may wish to modify or amend their approved applications. Investigators must seek IRB approval before making any changes in approved research - even though the changes are planned for the period for which IRB approval has already been given - unless the change is necessary to eliminate an immediate hazard to the participant (in which case the IRB must then be notified at once). Changes in approved research that are initiated without IRB approval to eliminate apparent immediate hazards to the participant are reviewed by the IRB to determine whether each change was consistent with ensuring the participants’ continued welfare.

Amendments may make changes to the protocol for all remaining participants or circumstances in which the specific procedures called for in a protocol are not applicable or in the best
interests of a specific participant or group of participants (for example: participant is allergic to one of the medications provided as supportive care). Usually an Exception is a change that is planned and has prior agreement from the sponsor. See Section 7.8.5 for details on Protocol Exceptions.

(Note: Protocol Deviations [see Section 14.1] are unplanned and are reported to the IRB after the fact.)

Investigators should consider whether the proposed changes to the research alter the original scope, purpose, or intent of the research. When the research itself is fundamentally changed, the IRB usually requires a new study application rather than allow such changes to be made through an amendment to the existing research plan.

7.8.1 Procedures

Investigators must submit documentation to inform the IRB about the proposed changes to the study, including, but not limited to:

- Completed Modification ‘smart form’ in Rapport;
- If the modification involves changes to the protocol, a revised protocol (with changes tracked or with a detailed summary of changes and the locations of those changes);
- If the modification involves changes to the consent/permission/assent documents, revised consent/parental permission/assent documents with changes tracked;
- If the modification involves changes to other study materials, the revised materials with changes tracked;
- Other documentation proposed to be provided to participants when the proposed change(s) to the research might relate to their willingness to continue to participate in the study; and
- Any other relevant documentation provided by the sponsor or coordinating center.

The Rapport modification smart form requests information specific to the modification. IRB staff reviews the submission and makes an initial determination whether the proposed change(s) may be approved through an expedited review process, if the changes are minor, or whether the modification warrants convened board review. The reviewer(s) using the expedited procedure has the ultimate responsibility to determine that the proposed change(s) may be approved through the expedited review procedure and, if not, must refer the research study for convened board review.

7.8.2 Convened IRB Review of Modifications

When a proposed change in a research study is not minor, the convened IRB must review and approve the proposed change at a convened meeting before the change can be implemented. The only exception is a change necessary to eliminate apparent immediate hazards to the
research participants. In such a case, the IRB should be promptly informed of the change following its implementation and should review the change to determine that it is consistent with ensuring the participants' continued welfare.

All IRB members are provided and review all documents provided by the investigator.

At the meeting, the Reviewer presents an overview of the proposed changes and assists the IRB Chair in leading the IRB through the completion of the regulatory criteria for approval. The IRB also determines whether the research with the proposed changes continues to meet the regulatory criteria for approval. The IRB considers whether information about the changes might relate to participants’ willingness to continue to take part in the research and if so, whether to provide that information to past/current/future participants.

**7.8.3 Expedited Review of Modifications**

An IRB may use expedited review procedures to review minor changes in ongoing previously-approved research during the period for which approval is authorized. An expedited review may be carried out by the IRB Chair and/or experienced designee(s) among the IRB members.

The reviewer(s) determines whether the amendment meets the criteria allowing review using the expedited procedure, and if so, whether the research with the proposed modifications continues to meet the regulatory criteria for approval. The reviewer also considers whether information about the changes might relate to participants’ willingness to continue to take part in the research and if so, whether to provide that information to past/current/future participants.

**7.8.4 Possible IRB Actions after Amendment Review**

The Convened IRB or IRB Member(s) conducting expedited review may take any of the following actions (See Section 7.6 for a detailed description of these actions):

1. Approve
2. Modifications Required to Secure Approval (MRSA)
3. Disapprove*

*Only the convened IRB may vote to disapprove the proposed change(s). If an IRB member conducting expedited review believes that the proposed change should be disapproved, the amendment is referred to the convened IRB for review.

If the proposed change(s) raise significant concerns on the part of the IRB, the IRB may vote to suspend or terminate the research (See Section 8 for a detailed discussion of suspensions and terminations).

**7.8.5 Prospective Protocol Deviation**

Prospective Protocol deviations are circumstances in which the investigator wishes to deviate from eligibility criteria or one or more of the specific procedures called for in a protocol. Unlike
changes that apply to all subsequent participants in the research, a deviation only applies to a specific participant or group of participants.

Deviations are planned, and the investigator gets approval from the sponsor, if applicable, and the IRB ahead of time. Depending on the nature of the deviation, an expedited review may be possible. In order to be approved under expedited review the deviation must not increase risk or decrease benefit, change the risk/benefit analysis, negatively affect the participant’s rights, safety or welfare, or negatively affect the integrity of the study data. Review of deviations that represent more than a minor change or risk level greater than minimal should be reviewed at a convened IRB meeting.

Procedures for prospective protocol deviations are the same as for a Protocol Modification. The investigator must submit a modification application, along with any revised documentation to be presented to the participant(s) and documentation of sponsor approval, if applicable.

The only time a protocol/Research Plan deviation does not require prior sponsor and IRB approval is when the deviation is necessary to avoid an immediate hazard to the participant. In such cases, the deviation must be submitted to the IRB as soon as possible.

### 7.9 Closing a Research Study

The completion or early closure of the study should be reported to the IRB with the Closure Form.

Studies may be closed when the involvement of human participants ceases (interventions, interactions, observations, and the gathering, use, study, and analysis of identifiable private information, including specimens, are all complete). Studies may also be closed when the only remaining research activity involves the analysis of unidentifiable individual level data, or aggregate data sets.

For multi-center research, the study may be closed once all research activities (as above) are complete at Dartmouth or any site for which the Dartmouth IRB is the “IRB of record”. If the investigator is serving as the lead investigator or Dartmouth is the coordinating center the study must remain open as long as the coordinating center is still receiving, studying, using, or analyzing identifiable private information from other sites (even if local interventions, interactions, observations, and data gathering are complete).

Investigators may maintain the data that they collected, including identifiable private data, if this is consistent with the IRB-approved research plan. However, investigators may not conduct any additional analysis of identified data without re-applying for IRB approval. Investigators must continue to protect the confidentiality of the data as described to the IRB and honor any other commitments that were agreed to as part of the approved research including, for example, future use of data or specimens, provision of research results to participants, and provision of any outstanding payments or compensation.
7.10 Reporting IRB Actions

All IRB actions are communicated to the investigator, and designated research staff, as applicable. The investigator receives electronic and written notification of approval. All approved documents are available electronically. If applicable, a copy of the approved consent/permission/assent form(s) contain the IRB stamp with the approval and expiration dates. For revisions required, the notification identifies all conditions that must be satisfied and additional information requested. When a study is disapproved, terminated or suspended, the notification includes the basis for the decision. The investigator may respond in person or in writing.

All letters, notices and reminders to investigators are maintained in the electronic study file. The IRB reports its findings and actions to the organization in the form of its minutes, which are distributed by IRB staff to the Dartmouth IO.

7.11 Responding to IRB inquiry

When research has IRB approval, and the investigator does not respond to requirements related to a subsequent submission (e.g., a request for modification), the IRB Staff or Chair may review the circumstances, including any potential impact on human participants, and contact the investigator to try to secure a response. If the investigator continues to be unresponsive, the failure of the investigator may be considered non-compliance and be reviewed in accordance with the procedures in Section 16. The investigator receives notification of non-compliance, including an explanation. An extension may be granted by the IRB if sufficient cause is provided by the investigator.

7.12 Appeal of IRB Decisions

When the IRB disapproves a study the IRB notifies the investigator in writing of the reason(s) for the decision and any modifications that are necessary for IRB approval. When research is suspended in part or in full, or terminated, the IRB notifies the investigator in writing of the suspension or termination and the reason(s) for the decision. The investigator may ask that the decision be reconsidered by submitting a request in writing to the IRB Chair. The request must contain the basis for the appeal, including any substantive new information that the Board did not have the opportunity to consider previously. The request is scheduled for review at a convened IRB meeting and the Investigator invited to attend the meeting.

Where there is disagreement between the IRB and the investigator regarding the nature and extent of the requested changes or the necessity of or basis for a suspension or termination, and these disagreements cannot be resolved, the investigator and/or the IRB may make an appeal to the IO for a resolution of the matter. The IO may organize a meeting to help facilitate discussion between the IRB and the investigator. While the IO may provide input and make recommendations to the investigator and IRB for expeditious resolution of the matter, final determinations for approval/disapproval remain under the purview of the IRB.
Because the IO is responsible for policies and procedures followed by the IRB, the IO may review IRB decisions to ensure that the decision-making process is appropriate. If the IO has concerns regarding the process that the IRB followed in making a decision, the IO may ask the IRB to reconsider the decision. However, the IO cannot overrule an IRB decision.

7.13 Research Previously Approved By Another IRB

When an investigator transfers research to Dartmouth that was previously approved by another IRB, the investigator must submit the research for review under the procedures covered by this section. No research activity may take place under the jurisdiction of Dartmouth without the appropriate review and approval.

Research approved as exempt at the previous institution is reviewed according to the procedures in Section 6. All other research must be submitted as if it were undergoing initial review and is reviewed by expedited review or by the convened IRB. Research that solely involves the analysis of existing identifiable data may be considered under Expedited Review Category 5.

For research transfers where stopping research interventions might harm participants, the investigator may request permission from the IRB to continue research interventions under the oversight of the prior organization’s IRB until final Dartmouth approval is obtained.

8 Study Suspension, Termination and Investigator Hold

8.1 Suspension/Termination

IRB approval may be suspended or terminated if research is not being conducted in accordance with IRB or regulatory requirements or has been associated with unexpected problems or serious harm to subjects. (See Section 15 for a discussion of unanticipated problems and Section 16 for a discussion of non-compliance.)

Suspension of IRB approval is a directive of the convened IRB or IRB Chair to temporarily stop some or all previously approved research activities. Suspensions made by the IRB Chair are reported to a meeting of the convened IRB. If IRB approval of a suspended research study expires and the suspension is lifted, a continuing review is required before the study may resume. Investigators must continue to provide reports on adverse events and unanticipated problems to both the IRB and sponsors just as if there had never been a suspension (i.e., all events that need to be reported during a study need to continue to be reported during the suspension period).

When approval of some or all research activities is suspended by the IRB, the IRB considers whether notification of study participants is required and any actions necessary to ensure that the rights, safety, and welfare of participants are appropriately protected.

The IRB shall notify the investigator in writing of a suspension and shall include a statement of the reasons for the IRB’s actions and any requirements or conditions associated with the
suspension (e.g., notification of participants). The investigator shall be provided with an opportunity to respond in person or in writing.

Suspensions of IRB approval are reported promptly to the Dartmouth IO, Department Chair, Office of Integrity and Compliance and Sponsored Programs Office, study sponsor(s), including federal department or agency heads, as applicable and federal oversight agencies according to applicable federal and organizational requirements. See Section 14 for a detailed discussion of reporting requirements.

**Termination** of IRB approval is a directive of the convened IRB to permanently stop all activities in a previously approved research study. Terminated research studies are closed. When study approval is terminated by the IRB, in addition to stopping all research activities, the IRB considers whether notification of participants is required and any actions necessary to ensure that the rights, safety, and welfare of research participants are appropriately protected.

The IRB shall notify the investigator in writing of a study termination and shall include a statement of the reasons for the IRB's actions and any requirements associated with the termination (e.g., notification of participants). The investigator shall be provided with an opportunity to respond in person or in writing.

Terminations of IRB approval are reported promptly to the Dartmouth IO, Department Chair, Office of Integrity and Compliance and Sponsored Programs Office, study sponsor(s), including federal department or agency heads, as applicable, and federal oversight agencies according to applicable federal and organizational requirements. See Section 14 for a detailed discussion of reporting requirements.

Note: Suspension or termination of research studies approved by the IRB can also be issued by Organization officials acting outside of and unrelated to the interests of the IRB (i.e., not necessarily related to protecting the rights and welfare of study participants). Such Organization actions can be made by, for example, the IO, Department Chairs or School Deans. The investigator must report any suspension or termination of the conduct of research to the IRB. The IRB determines if suspension or termination of IRB approval is warranted and notifies the Investigator.

### 8.2 Investigator Hold

An investigator may request an investigator hold when the investigator wishes to temporarily or permanently stop some or all approved research activities. Such a hold should be immediately reported to the IRB so that the IRB can consider whether any additional actions are necessary to protect research participants. Investigator holds are not equivalent to IRB suspensions or terminations.

#### 8.2.1 Procedures

1. Investigators submit an amendment to the IRB that includes (as applicable):
   a. A description of the research activities to be stopped;
   b. Proposed action(s) to be taken to protect current participants;
c. Action(s) to be taken prior to IRB approval of proposed changes in order to eliminate apparent immediate risk of harm.

2. Upon receipt of the amendment it is either placed on the agenda of the next available IRB meeting for review (greater than minimal risk studies) or referred to the IRB Chair or designee for review (minimal risk studies).

3. For greater than minimal risk studies, the IRB determines whether any additional procedures need to be followed to protect the rights and welfare of current and/or former participants. For minimal risk studies, the IRB Chair or designee, in consultation with the IRB Office Director and/or staff and investigator, determines whether any additional procedures need to be followed to protect the rights and welfare of current and/or former participants. (See Section 8.3).

4. For greater than minimal risk studies, the IRB determines if currently enrolled participants and/or former participants should be notified of the hold, and if notified, how and when. For minimal risk studies, the IRB Chair or designee, in consultation with the IRB Office Director and/or staff and investigator, determine if currently enrolled participants and/or former participants should be notified of the hold, and if notified, how and when.

5. Investigators may request a revision of the research on hold by submitting a request for revisions to previously approved research.

8.3 Protection of Currently Enrolled and Former Participants

Before a study hold, termination, or suspension is put into effect the IRB Chair or IRB considers whether any additional procedures need to be followed to protect the rights and welfare of current and/or former participants. Such procedures might include:

- Transferring participants to another investigator/site
- Making arrangements for clinical care outside the research
- Allowing continuation of some research activities under the supervision of an independent monitor
- Requiring or permitting follow-up of participants for safety reasons
- Requiring adverse events or outcomes to be reported to the IRB and the sponsor
- Notification of current participants
- Notification of former participants

9 Reliance on External IRB Review

9.1 External IRB review

Dartmouth investigators wishing to conduct industry-sponsored, industry-initiated biomedical research studies at Dartmouth may request a reliance on a commercial/independent or other external IRB.
9.1.1 Investigator Responsibilities

1. Submit the application package to the external IRB, following all external IRB and sponsor requirements.

2. Once approval has been obtained from the external IRB, submit the following to the Dartmouth IRB:
   a. And complete applicable Rapport Smart Forms;
   b. Sponsor Protocol/research plan; and
   c. Sponsor approved consent/permission/assent documents.

9.1.2 Dartmouth Responsibilities Prior to Accepting External Oversight for a Study

The following materials are reviewed:

- Eligibility for external IRB review
- Investigator and study staff documentation as applicable
- Involvement of special populations, e.g., minors or adults not able to give consent form themselves
- HIPAA compliance as applicable
- Ancillary approvals and organizational processes for financial disclosure/COI management requirements, budget review and contract negotiation, and other required committee or ancillary reviews as applicable are either in process or completed.
- Review by IRB Director, Chair, or designee

9.1.3 Dartmouth Responsibilities Post Approval

Dartmouth retains certain on-site responsibilities for all studies where Dartmouth relied upon external IRB review. Reports of site monitoring activities which have any findings that potentially impact human subject protections must be shared between the external IRB and Dartmouth.

The IRB Reliance Agreement outlines roles and responsibilities which may include investigator reporting changes to the study, including changes in study personnel, prior to the personnel assuming any study responsibilities, local unanticipated problems, complaints, and non-compliance.

9.2 National Cancer Institute’s Central IRB Adult and Pediatric Initiative

Dartmouth is a participant in the National Cancer Institute’s Central Institutional Review Board (CIRB) Initiative for cooperative group protocols/studies that have been reviewed and approved by the CIRB. Dartmouth’s IRB Office submits the necessary documentation to maintain
institutional registration with the CIRB, including the “Authorization Agreement/Division of Responsibilities”, the listing of Key Personnel, and the “Annual Signatory Institution Worksheet About Local Context”.

The CIRB defers responsibility to local institutions to conduct any reviews necessary under HIPAA, but accepts institutional boilerplate language for HIPAA authorizations if an institution incorporates authorization into research consent documents. HIPAA authorization language is included in the Dartmouth NCI CIRB “Annual Signatory Institution Worksheet About Local Context”.

The CIRB relies on local institutions to identify potential conflicts of interest and to develop conflict management plans. Dartmouth investigators submit disclosures to the Office of Cancer Research (OCR), identify potential COI on the IRB application and submit proposed management plans received from the OCR. Investigators must submit conflict management plans for themselves or members of the local research team to the CIRB using the “Annual Principal Investigator Worksheet About Local Context” or the “Study-Specific Worksheet About Local Context”.

9.2.1 Investigator Responsibilities:

1. Complete, on an annual basis, the “Annual Principal Investigator Worksheet About Local Context” and submit to the Cancer Center Office of Clinical Research (OCR) and the CIRB. Once CIRB-approved, the investigator may proceed with individual study applications.

2. In order to open individual protocols/studies under the CIRB, the investigator:
   a. Submit the application package to the NCI CIRB, following all NCI CIRB requirements.
   b. Once approval has been obtained from the NCI CIRB, submit the following to the Dartmouth IRB:
      i. Dartmouth IRB application: The study is reviewed to ensure that all applicable training/credentialing requirements have been satisfied, and to assess the impact of the proposed activity on Dartmouth patients, services and facilities;
      ii. Sponsor Protocol/research plan;
      iii. NCI CIRB approval letter; and
      iv. Sponsor approved consent/permission/assent documents with required local institutional language incorporated.
9.2.2 Dartmouth Responsibilities Prior to Institutional Study Approval

Dartmouth reviews the application and supporting documentation. Once determined to be acceptable, with any applicable ancillary reviews satisfied, the investigator is notified that he/she may begin the study at Dartmouth. Additional reminders of local policies concerning special topics (assent, incapacitated adults, etc.) and Investigator Responsibilities may also be included in the notification.

9.3 Ongoing responsibilities after study approval:

1. By written agreement with the CIRB, the Cancer Center Office of Clinical Research (OCR) is responsible for ensuring compliance with the regulations governing research and the determinations made by the CIRB, and to report possible serious or continuing non-compliance and unanticipated problems to the CIRB for evaluation. In order to fulfill these responsibilities the Cancer Center Office of Clinical Research (OCR) maintains current documentation of the study, the actions taken by the CIRB, and any local issues that arise with the research. The investigator submits the following to the Cancer Center Office of Clinical Research (OCR) on an ongoing basis and reports to the IRB as needed:

   a. Amended protocols/research plans, investigator brochure(s), local consent documents, translated consent documents, local advertisements, recruitment tools, and patient materials, and the associated documentation of CIRB approval;
   
   b. Audit reports;
   
   c. Local unanticipated events, protocol/research plan exceptions, and protocol/research plan deviations;
   
   d. Local participant complaints or unresolved concerns;
   
   e. Changes in local study personnel;
   
   f. Changes in study status locally and study-wide (Open to Enrollment, Closed to Enrollment, Suspended, etc.);
   
   g. Conflict of Interest disclosures within 30 days of a change in significant financial interests or circumstances that could represent a conflict of commitment;
   
   h. An annual summary of study activity describing the number of local enrollees and status of enrollees (screen failure, on treatment, on follow up, withdrawn, complete, deceased), the study status (open to enrollment, closed to enrollment – active treatment, closed to enrollment – follow up only, closed to enrollment – data analysis, all local activities complete (closed)), any shifts in the evidence or in standard care that could impact the target study population or enrollment into the study, and any local complaints, concerns, or problems with the research.
2. The Cancer Center Office of Clinical Research (OCR) staff reviews submissions, verifies current training (CITI or accepted alternative) for each member of the local research team and seeks additional information, if needed, from the local research team. The local research team reports potential unanticipated problems, potential serious or continuing non-compliance, local suspensions or terminations of research activities, and audit reports that note regulatory deficiencies to the CIRB, OCR and IRB as required. The report includes, if applicable, a corrective and preventative action plan (CAPA) developed in cooperation with the Investigator. The CIRB makes a final determination regarding whether or not such events are unanticipated problems involving risks to participants or others, serious non-compliance, or continuing non-compliance and initiates any necessary reporting to sponsors and federal agencies.

3. Local investigators are responsible for submitting any COI management plans, translated consent forms (with accompanying certificate of translation), local participant materials, and local advertisements and recruitment materials to the CIRB.

4. Research open under the CIRB remains subject to Dartmouth institutional and HRPP policies and procedures, including, but not limited to, internal and external audits, training requirements, advertisements, privacy, and confidentiality.

10 Documentation and Records

Dartmouth’s IRB Office maintains adequate documentation of the IRB’s activities. All records are accessible for inspection and copying by authorized representatives of the FDA, OHRP, sponsors, and other authorized entities at reasonable times and in a reasonable manner.

10.1 IRB Records

IRB records include, but are not limited to:

1. Written operating procedures
2. IRB membership rosters
3. Training records documenting that investigators, IRB members, and IRB staff have fulfilled Dartmouth’s human research training requirements
4. IRB correspondence including reports to regulatory agencies
5. IRB Study Records (Study Files) including correspondence with investigator and research team
6. Documentation of exemptions granted
7. Documentation of reports of emergency use
8. Convened IRB meeting minutes
9. Documentation of review by another institution’s IRB, when appropriate
10. Documentation of cooperative review agreements, including Memoranda of Understanding (MOUs), Authorization Agreements (AAs) and Reliance Agreements.
11. Dartmouth’s Federalwide Assurance
12. IRB Registrations
13. Documentation of complaints and any related findings and/or resolution

10.2 IRB Study Files

The IRB maintains a separate electronic IRB study file for each research application (study) that it receives for review. Research studies are submitted through the IRB electronic system and assigned a unique identification number by the system.

Accurate records are maintained of all communications to and from the IRB and are a part of the electronic study file. Dartmouth’s IRB maintains a separate file for each research study that includes, but is not limited to:

1. Research plan and all other documents submitted as part of a new study application
2. Research plan and all other documents submitted as part of a request for continuing review or Final Report
3. Documents submitted and reviewed after the study has been approved, including requests for revisions, proposed advertisements, data and safety monitoring reports, and reports of protocol/research plan violations, complaints, non-compliance, unanticipated adverse device events and unanticipated problems
4. Copy of IRB-approved Consent/Assent/Authorization Forms
5. DHHS-approved sample consent form document and research plan, when applicable
6. Documentation of scientific or scholarly review (if available) [Department Review Form]
7. Documentation of type of IRB review. For exempt determinations and expedited review, this includes the category under which the review is allowed.
8. For expedited review, documentation (on the study approval letter) of any findings and determinations required by the regulations and study-specific findings supporting those determinations, including, but not limited to, waiver or alteration of consent, waiver of documentation of consent, research involving pregnant women, fetuses, and neonates, research involving prisoners, and research involving children. For research reviewed by the convened board these findings and determinations are recorded in the minutes.
9. For expedited review, documentation (on the study approval letter) of the risk determination and period of approval. For research reviewed by the convened board these determinations are recorded in the minutes.
10. Documentation of all IRB review actions
11. Copies of IRB approval letters
12. IRB correspondence to and from Investigators
13. Notification of expiration of IRB approval to the Investigator and requirements related to the expiration as applicable
14. Notification of suspension or termination of research
15. A description of any requirements that the Investigator must satisfy before beginning the study
16. All other IRB correspondence related to the research
17. For devices, documentation of determination by IRB of significant risk/non-significant risk (NSR / SR CPHS Form)
18. Reports of unanticipated problems involving risk to subjects or others
19. Documentation of audits, investigations and reports of external site visits

10.3 The IRB Minutes

Proceedings are written by CPHS Analysts and available for review by the IRB Chair and members.
A copy of IRB minutes for each IRB meeting are made available to the IO.

Minutes of IRB meetings contain sufficient detail to show:

1. Attendance
   a. Names of members and alternates present
   b. Names of members and alternate members who are participating through videoconference or teleconference.
   c. Names of alternate(s) attending in lieu of absent members.
      Note: The attendance list identifies members present. The vote on each action, documented electronically, reflects the number of members present for the vote on each item. The name of each member present for the vote of each item is also documented electronically, as well as the name of each member who recuses himself or herself because of a conflict of interest.
   d. Names of consultant(s) present
   e. Names of investigators present
   f. Names of guests present

2. The presence of a quorum throughout the meeting, including the presence of one member whose primary concern is in a non-scientific area.

3. Administrative items reviewed or discussed

4. Continuing Education
5. Actions taken, including separate deliberations, actions, and votes for each research study undergoing review by the convened IRB.

6. Vote counts on each action (Total Number voting; Number voting for; Number voting against; Number abstaining; Number recused)

7. Basis or justification for actions disapproving or requiring changes in research

8. Summary of controverted issues and their resolution

9. Approval period for initial and continuing reviews, including identification of research that warrants review more often than annually and the basis for that determination

10. Risk determination for initial and continuing reviews, and modifications when the modification alters the prior risk determination

11. Justification for deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample consent document.

12. Study-specific findings supporting that the research meets each of the required criteria when approving a consent procedure that does not include or that alters some or all of the required elements of informed consent, or when waiving the requirement to obtain informed consent altogether

13. Study-specific findings supporting that the research meets each of the required criteria when the requirements for documentation of consent are waived

14. Study-specific findings supporting that the research meets each of the criteria for approval for vulnerable populations under any applicable Subparts

15. Significant risk/non-significant risk device determinations and the basis for those determinations

16. Determinations of conflict of interest and acceptance or modification of conflict management plans

17. Identification of any research for which there is need for verification from sources other than the investigator that no material changes are made in the research.

18. Review of interim reports, e.g., unanticipated problems or safety reports; modification requests; report of violation/deviations; serious or continuing non-compliance; suspensions/terminations, etc.

19. A list of research approved under expedited review procedures since the last report

20. When an IRB member or alternate has a conflict of interest (see Section 21.2) with the research under review, an indication that the IRB member or alternate was not present during the final deliberation or vote

21. Key information provided by consultants, either in person or in a report
10.4 IRB Membership Roster

A membership list of IRB members is maintained and submitted to OHRP as required. The list contains the following information about members:

1. Name
2. Earned degree(s)
3. Employment or other relationship between each member and the organization (i.e., affiliated or non-affiliated). To be categorized as non-affiliated, neither the member nor an immediate family member of the member may be affiliated with Dartmouth.
4. Status as scientist or non-scientist. Members whose training, background, and occupation would incline them to view scientific activities from the standpoint of someone within a behavioral or biomedical research discipline are considered a scientist for the purposes of the roster, while members whose training, background, and occupation would incline them to view research activities from a standpoint outside of any biomedical or behavioral scientific discipline are considered a nonscientist.
5. Indications of experience, such as board certifications, licenses, and areas of practice sufficient to describe each member's chief anticipated contributions to IRB deliberations.
6. Representative capacities of each IRB member; including which IRB member(s) is a prisoner representative, and which IRB members are knowledgeable about or experienced in working with children, pregnant women, cognitively impaired individuals, and other vulnerable populations commonly involved in Dartmouth research.
7. Role on the IRB (Chair, Member, Alternate Member)
8. Voting status
9. For alternate members, the primary member or class of members for whom the member could substitute

The IRB office must keep the IRB membership list current. The IRB Office reports changes in IRB membership to OHRP/FDA within 90 days of the change.

10.5 Documentation of Exemptions

Documentation via study approval letter of verified exemptions consists of the reviewer’s citation of a specific exemption category and written determination that the activity described in the investigator’s proposed study meets the conditions of the cited exemption category, as detailed in Section 6.

10.6 Documentation of Expedited Reviews

IRB records for initial and continuing review by the expedited procedure include: the specific permissible category; that the activity described by the investigator satisfies all of the criteria for approval; the approval period and any determinations required by the regulations including study-specific findings justifying the following determinations:
1. Approving a procedure which waives or alters the informed consent process;
2. Approving a request for waiver or alteration of the requirement for documentation of consent;
3. Approving research involving pregnant women, human fetuses, or neonates;
4. Approving research involving children.
5. Approving research involving participants with diminished capacity.

10.7 Access to IRB Records

The IRB has policies and procedures to protect the confidentiality of research information:

1. Paper IRB records are kept secure in filing cabinets. Doors to the IRB Offices are closed and locked when the rooms are unattended. The electronic management system, Rapport, is a password only accessible management system.
2. Ordinarily, access to all IRB records is limited to the IRB Office Director and Staff, IRB Chair, IRB members, authorized organizational officials, and officials of federal and state regulatory agencies (e.g., OHRP and FDA). Research investigators are provided reasonable access to files related to their research. Appropriate accreditation bodies are provided access. All other access to IRB records is limited to those who have legitimate need for them, as determined by the IO and Director.
3. Records are accessible for inspection and copying by authorized representatives of federal regulatory agencies during regular business hours.
4. Paper records may not be removed from the IRB Office; however, the IRB staff provides copies of records for authorized personnel if requested.
5. All other access to IRB study files is prohibited.

10.8 Record Retention

In order to comply with the requirements of OHRP, FDA, HIPAA and the Dartmouth record retention policy IRB records are maintained for at least six (6) years after completion of the research.

11 Obtaining Informed Consent from Research Participants

No investigator conducting research under the jurisdiction of Dartmouth may involve a human being as a research participant without obtaining the legally effective informed consent of the participant or the participant’s legally authorized representative unless a waiver of consent has been approved by the IRB in accordance with Section 11.9. Except as provided in Sections 11.10 and 11.11, informed consent must be documented by the use of a written consent form approved by the IRB.
The IRB evaluates both the consent process and the procedures for documenting informed consent to ensure that adequate informed consent is obtained from participants.

The following procedures describe the requirements for obtaining consent from participants in research conducted under the auspices of Dartmouth.

11.1 Definitions

Legally Authorized Representative: A legally authorized representative (LAR) is an individual or body authorized under applicable law to provide permission on behalf of another. As of January 2015, NH State Law restricts enrollment into “experimental treatment.” See definition below. Please carefully review the revised CPHS Form entitled: Research Involving Individuals Lacking Decision-Making Capacity.”

Legal guardian: A person appointed by a court of appropriate jurisdiction.

Experimental Treatment: CPHS has defined experimental treatment within NH State law as a treatment that is unproven or not yet scientifically validated with respect to safety and efficacy. A treatment is defined as a drug, device or procedure intended to alleviate a disease or disorder. See Section 12.8 for additional information.

11.2 Basic Requirements

The requirement to obtain the legally effective informed consent of an individual before involving him/her in research is one of the central protections provided for by the Federal regulations and Dartmouth’s IRB. When informed consent is required, it must be sought prospectively, and properly documented.

The informed consent process involves three key features: (1) disclosing to the prospective research participant information needed to make an informed decision; (2) facilitating the understanding of what has been disclosed; and (3) promoting the voluntariness of the decision about whether or not to participate in the research.

Informed consent is a process of information exchange that includes discussion, questions and answers and signing the consent document. The informed consent process is the critical communication link between the prospective research participant and an Investigator. The process begins when the participant first learns about the research and continues through the completion of the research study. The person obtaining consent must be sufficiently knowledgeable about the study to be able to answer questions and help potential study participants understand the study. Investigators must obtain consent prior to entering a participant into a study, gathering data about a participant, and/or conducting any procedures required by the research plan, including screening procedures, unless consent is waived by the IRB.

Study team members designated to obtain informed consent are named in Rapport.

Sample or draft consent documents may be developed by a sponsor or cooperative study group. However, when the Dartmouth IRB is the IRB of record for the study, the Dartmouth
IRBS is the final authority on the content of a consent document that is presented to a potential study participant.

These informed consent requirements are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed for informed consent to be legally effective.

11.3 Informed Consent Process

1. The potential participant must have the legal and mental capacity to give consent. For a participant without that capacity, permission must be obtained from a legally authorized representative.

1. The potential participant or the participant’s LAR must have sufficient opportunity to read the consent document, when applicable.

2. The potential participant or the participant’s LAR must be given sufficient opportunity to consider whether or not to participate.

3. The consent process shall be under circumstances that minimize the possibility of coercion or undue influence.

4. The consent information must be presented in language that is understandable to the potential participant or the participant’s LAR. To the extent possible, the language should be understandable by a person who is educated to 8th grade level and layman’s terms should be used in the description of the research.

5. If a participant’s native language is not English and the participant does not speak or understand English, informed consent must be obtained in a language that is understandable to the participant or the participant’s LAR. In accordance with this policy, the IRB requires that informed consent discussions include a reliable interpreter when the prospective participant does not understand the language of the person who is obtaining consent.

6. The informed consent process may not include any exculpatory language through which the participant is made to waive, or appears to waive any of his/her legal rights or through which the investigator, the sponsor, Dartmouth or Dartmouth employees or agents are released from liability for negligence, or appear to be so released.

7. The investigator or designee is responsible for ensuring that each prospective study participant is adequately informed about all aspects of the research and understands the information provided.

8. The IRB strongly encourages the use of the ‘teach back’ method during the consent process.

11.4 Determining a potential adult participant’s ability to consent to research

A potential research participant has the capacity to consent to his or her own participation in a research activity if he/she demonstrates an appreciation:
1. That the activity is research
2. Of the risks and benefits of a study
3. Of the study procedures and requirements
4. Of the alternatives that are available if not participating
5. That, by choosing not to participate, this decision is accepted without penalty

In reaching a decision about participation, it is essential for the potential participant to demonstrate an ability to use this information in a rational manner. Thus, in considering risks, benefits, and available alternatives, participants must show they understand the aspects of these factors that are unique to them as individuals.

See Section 12.8 for further discussion regarding adults who cannot give consent for themselves.

The decision-making capacity of a potential research participant should be evaluated when there are reasons to believe that the potential participant may not be capable of making voluntary and informed decisions about research participation. The investigator and research staff should have procedures in place for assessing and ensuring a participant’s capacity to understand and make an informed decision. The IRB evaluates whether the proposed plan to assess capacity to give consent is adequate. Reference: Research involving Individuals with Impaired Decision Making Capacity Form, Teach - Back

Investigators and IRB members must be aware that for some participants’ decision-making capacity may fluctuate. In the event that a research participant loses or becomes impaired in decision-making capacity after enrollment, and this is not anticipated in the research plan, the investigator is responsible for notifying the IRB. The investigator is responsible for developing a plan for the IRB’s consideration which follows the guidelines outlined above for persons with fluctuating or diminishing capacity.

When a participant has the capacity to give consent, informed consent should be obtained and documented in accordance with Section 11.6. When a participant lacks the capacity to give consent, investigators may obtain consent from the participant’s LAR as described in Section 12.8. When consent will be obtained from the participant’s LAR, the agreement of the participant should also be sought, if possible. If the investigator plans to use audio or videotapes, computer video presentations, or written materials, to promote understanding, these materials must be provided to the IRB for review. If the investigator intends to use audio or video recordings to document consent or agreement, provisions to ensure the security of the recordings should be described to the IRB.

11.5 Basic Elements of Informed Consent

To be valid, the consent process must provide the following basic elements of information to potential study participants:

1. 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;

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

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

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

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

6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects’ rights, and whom to contact in the event of a research-related injury to the subject;

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

9. For FDA-regulated studies, a statement that notes the possibility that the Food and Drug Administration may inspect the records;

10. For “applicable” FDA-regulated clinical trials, the following statement must be included:

“A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.”

In general, “applicable” clinical trials mean controlled clinical investigations, other than Phase 1 clinical investigations, of a drug or biologic; and prospective clinical studies of health outcomes comparing an intervention with a control (other than (i) small clinical trials to determine the feasibility of a device, (ii) a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes, or (iii) mandated pediatric postmarket surveillance activities)

Additional elements of informed consent to be applied, as appropriate:

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
2. Anticipated circumstances under which the subject’s participation may be terminated by the investigator without regard to the subject’s consent;
3. Any additional costs to the subject that may result from participation in the research;
4. The consequences of a subject’s decision to withdraw from the research and procedures for orderly termination of participation by the subject;
5. A statement that significant new findings developed during the course of the research which may relate to the subject’s willingness to continue participation will be provided to the subject;
6. The approximate number of subjects involved in the study.

11.6 Documentation of Informed Consent

Except as provided in Section 11.10, informed consent must be documented by the use of a written consent form approved by the IRB.

1. Informed consent is documented by the use of a written consent form approved by the IRB and signed and dated by the participant or the participant’s legally authorized representative at the time of consent. When regulatory required, the name of the individual obtaining consent is also identified on the consent form.
2. A copy of the signed and dated consent form is given to the person signing the form. The study team retains the signed original in the research records.
3. The consent form must be:
   a. A written consent document that embodies the basic and required additional elements of informed consent. The consent form may be read to the potential participant or the potential participant’s LAR, but the potential participant or LAR must be given adequate opportunity to read it before it is signed.

11.7 Special Consent Circumstances

11.7.1 Enrollment of persons with limited English-language proficiency

1. Expected enrollment: In some studies, the investigator may be able to anticipate enrollment of persons who do not speak or read, or have limited proficiency in, oral or written English. When the target population includes such persons or the investigator and/or the IRB otherwise anticipates that the consent process will be conducted in a language other than English, the IRB requires a translated consent document and other participant materials, to be prepared. In order to ensure that translated documents are accurate, the investigator may choose to provide a certified translation, or to provide a translated document with an independent back-translation. When a non-English speaking participant enrolls, the participant signs the translated consent document and is given a copy of the signed translated consent document.

2. Unexpected enrollment: If a person who does not speak or read, or has limited proficiency in, English presents for possible enrollment, an IRB-approved translated version of the written consent may not be available for use. Investigators should
carefully consider the ethical and legal ramifications of enrolling a participant when a language barrier exists. If the participant does not clearly understand the information presented during the consent process or in subsequent discussions, his/her consent may not be informed, and therefore, not effective.

3. **Use of interpreters in the consent process:** Unless the person obtaining consent is fluent in the prospective participant’s language, an interpreter is necessary to facilitate the consent discussion. Preferably someone who is independent of the participant (i.e., not a family member) should assist in presenting information and obtaining consent.

11.7.2 **Enrollment of persons who are blind**

For blind participants who read Braille, the IRB may approve a consent document prepared in Braille. In order to assure that a Braille consent document is accurate, the IRB may require a transcription into print text or review of the document by someone who reads Braille. If possible, the participant signs the Braille consent document; otherwise oral consent is obtained, witnessed and documented as described under “Oral Consent” (see Section 11.7.4).

11.7.3 **Enrollment of persons who are deaf**

For deaf participants who are fluent in American Sign Language (ASL), the IRB may approve a consent process using ASL and the IRB-approved written consent form. When this process is approved, the individual authorized to obtain consent from the prospective participant must use a certified interpreter fluent in ASL to conduct the consent process and the documentation of the consent process must conform to the requirements set forth in Section 11.6.

11.7.4 **Oral Consent**

When a potential participant is unable to read a written consent form (for example, is blind or illiterate), the IRB may approve an oral consent process, provided the potential participant (1) has the ability to understand the concepts of the study and evaluate the risk and benefit of being in the study when it is explained orally and (2) is able to indicate approval or disapproval to study entry.

For research that is no more than minimal risk, documentation of consent may be waived according to the criteria in Section 11.9.

For greater than minimal risk research, the consent form must be read to the potential participant and the participant must be given an opportunity to ask questions. An audiotape approved by the IRB may also be used. If capable of doing so, the participant signs, or marks an X to signify consent. If that is not possible, the participant provides oral consent. The person obtaining consent and a witness sign the written study consent form with a statement that documents that an oral process was used and, if necessary, that the participant gave oral
consent. The consent process is also documented in the participant’s research record. A signed copy of the consent form is given to the participant and a copy of the audiotape, if applicable.

11.8 Participant Withdrawal or Termination

A participant enrolled in a research study may decide to withdraw from the research, or an investigator may decide to terminate a participant’s participation in the research regardless of whether the participant wishes to continue participating. Investigators must plan for the possibility that a participant will withdraw from research and include a discussion of what withdrawal will mean and how it will be handled in the research protocol/research plan and consent document(s).

When seeking informed consent, the following information regarding data retention and use must be included:

- For FDA-regulated clinical trials, when a participant withdraws from a study, data collected on the participant prior to withdrawal remain part of the study database and may not be removed. The consent document cannot give the participant the option of having data removed.

- For research not subject to FDA regulations, the investigator should inform participants whether the investigator intends to: (1) retain and analyze already collected data relating to the participant up to the time of withdrawal; or (2) honor the participant’s request that the investigator destroy or exclude the participant’s data from any analysis.

When a participant’s withdrawal request is limited to discontinuation of the primary interventional component of a research study, research activities involving other types of participation for which the participant previously gave consent may continue if provided for in the research protocol/research plan. If so provided, the Investigator will ask the participant who is withdrawing whether the participant wishes to provide continued follow-up and further data collection subsequent to withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the participant will distinguish between study-related interventions and procedures and continued follow-up in person, by phone, or via record review, of data and address the maintenance of privacy and confidentiality of the participant’s information.

If a participant withdraws from the interventional portion of a study and does not consent to continued follow-up, the investigator must not access or gather additional private information about the participant for purposes related to the study. However, an investigator may review study data related to the participant collected prior to the withdrawal from the study, and may consult public records, such as those establishing survival status.
11.9 Waiver of Informed Consent

An IRB 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 IRB 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 will be provided with additional pertinent information after participation.

In addition, an IRB 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 IRB finds and documents that:

(a) The research or demonstration 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:
   1. Public benefit or service programs;
   2. Procedures for obtaining benefits or services under those programs;
   3. Possible changes in or alternatives to those programs or procedures; or
   4. Possible changes in methods or levels of payment for benefits or services under those programs; and,
(b) 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 certain emergency situations.

11.10 Waiver of Documentation of Informed Consent

The IRB may waive the requirement for the investigator to obtain a signed consent form for some or all participants if it finds either that the:

1. The only record linking the participant and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality;

   Note 1: Participants must be asked whether they want documentation linking them with the research, and their wishes must govern. (Example: domestic violence research where the primary risk is discovery by the abuser that the subject is talking to investigators.)
   Note 2: In order to waive written documentation of consent where the only record
linking the participant and the research would be the consent document, the IRB has to determine that the research is not FDA-regulated.

or

2. The research presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context. Procedures such as non-sensitive surveys, questionnaires and interviews generally do not require written consent when conducted by non-investigators (e.g., marketing surveys, telemarketing). Note: The FDA does permit a waiver of documentation of consent if this condition is satisfied. This is most commonly applied in the context of minimal risk screening activities that are necessary to determine eligibility for enrollment in the full trial.

Unless the IRB has granted a full waiver of the requirement to obtain informed consent, investigators who seek and receive approval for a waiver of documentation of consent still must perform an adequate consent process.

In cases in which the documentation requirement is waived, the IRB requires the investigator to provide in the application materials a written summary of the information to be communicated to participants, and the IRB considers whether to require the investigator to provide participants with a written statement regarding the research. See CPHS Information Sheet template.

11.11 Waiver of Informed Consent for Planned Emergency Research

The conduct of planned research in life-threatening emergencies where the requirement to obtain prospective informed consent has been waived by the IRB is covered by 21 CFR 50.24 for FDA-regulated research and by the waiver articulated by DHHS at 61 FR 51531-33 for non-FDA-regulated research.

The FDA exception from informed consent requirements for emergency research, 21 CFR 50.24, permits planned research in an emergency setting when human participants who are in need of emergency medical intervention cannot provide legally effective informed consent themselves and there is generally insufficient time and opportunity to locate and obtain consent from their LAR.

The Secretary of Health and Human Services (DHHS) has implemented an Emergency Research Consent Waiver under 45 CFR 46.101(i), with provisions equivalent to those of the FDA with the exception of the requirements specified in Sections 11.11.2.1 and 11.11.2.2 below. The DHHS waiver is not applicable to research involving prisoners, pregnant women, fetuses, or in vitro fertilization.

11.11.1 Definitions

Planned Emergency Research: Research that involves participants who are in a life-threatening situation for which available therapies or diagnostics are unproven or unsatisfactory and
because of the participants' medical condition and the unavailability of LARs it is generally not possible to obtain legally effective informed consent.

**Family Member:** For this section means a legally competent adult with one of the following relationships to the participant: spouse; parent; child (including adopted children); siblings and spouses of siblings; and any individual related by blood or affinity whose close association with the participant is the equivalent of a family relationship.

### 11.11.2 Procedures

The IRB may approve the planned emergency research without requiring informed consent of all research participants prior to initiating the research intervention if the IRB finds and documents that the following conditions have been met:

1. The participants are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

2. Obtaining informed consent is not feasible because:
   
   (i) Participants will not be able to give informed consent as a result of their medical condition;
   
   (ii) The intervention under investigation must be administered before consent from the participant’s LAR is feasible; and
   
   (iii) There is no reasonable way to prospectively identify the individuals likely to become eligible for participation in the research.

3. Participation in the research holds out the prospect of direct benefit to participants because:
   
   (i) Participants are facing a life-threatening situation that necessitates intervention;
   
   (ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual participant; and
   
   (iii) Risks associated with the research are reasonable in relation to what is known about the medical condition of the potential class of participants, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

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

5. The proposed research plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a LAR for each participant within that window of time and, if feasible, to ask the LAR contacted for consent within that window rather than proceeding without consent. The investigator will
summarize efforts made to contact LARs and make this information available to the IRB at the time of continuing review.

(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Sections 46.116 and 46.117 of 45 CFR 46 and Sections 50.20, 50.25 and 50.27 of 21 CFR 50. These procedures and the informed consent document are to be used with participants or their LAR in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a participant's participation in the research consistent with paragraph (7)(v) of this section.

(7) Additional protections of the rights and welfare of the participants will be provided, including, at least:

(i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the community(ies) in which the research will be conducted and from which participants will be drawn;

(ii) Public disclosure to the community(ies) in which the research will be conducted and from which participants will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;

(iii) Public disclosure of sufficient information following completion of the research to apprise the community, the public and researchers of the study's results, including the demographic characteristics of the research population, and its results;

(iv) Establishment of an independent data monitoring committee to exercise oversight of the research; and

(v) When obtaining informed consent is not feasible and a LAR is not reasonably available, the investigator has committed, if feasible, to attempt to contact a non-LAR family member of the potential participant within the potential therapeutic window and ask whether he or she objects to the participant's participation in the research. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

The IRB will ensure that procedures are in place to inform, at the earliest feasible opportunity, each participant, or, if the participant remains incapacitated, the participant’s LAR, or if such a representative is not reasonably available, a family member, of the participant’s inclusion in the research, the details of the research and other information contained in the informed consent document, including participation may be discontinued at any time without penalty or loss of benefits to which the participant is otherwise entitled. If a LAR or family member is told about the research and the participant’s condition improves, the participant is informed as soon as feasible. If a participant is entered into research with waived consent and the participant dies before a LAR or family member can be contacted, information about the research is provided to the LAR or family member, if feasible.
11.11.2.1 FDA-regulated Planned Emergency Research

1) A licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation must concur that the conditions described in Section 11.11.2 are satisfied.

2) Studies involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies that such studies may include participants who are not able to give consent. The submission of those studies in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under 312.30 or 812.35.

3) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided in the regulations or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to the FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

4) The IRB determinations and documentation required in Section 11.11.2 and paragraph 3 are retained by the IRB in an electronic format indefinitely, and available for inspection and copying by FDA in accordance with 56.115(b).

11.11.2.2 Planned Emergency Research Not Subject to FDA Regulations

The IRB responsible for the review, approval, and continuing review of the research has approved both the research and a waiver of informed consent and has (i) found and documented that the research is not subject to regulations codified by the FDA at 21 CFR Part 50, and (ii) found and documented and reported to the OHRP that the conditions required in Section 11.11.2 have been met.

12 Vulnerable Research Participants

When some or all of the participants in a research study conducted under the jurisdiction of Dartmouth are likely to be vulnerable to coercion or undue influence or have diminished decision-making capacity, the research must include additional safeguards to protect the rights and welfare of these participants. The IRB must ensure that all of the regulatory requirements for the protection of vulnerable participants are met and that appropriate additional protections for the vulnerable population are in place.
12.1 Definitions

Children. Children are 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 is conducted.

According to New Hampshire law, a person may consent to his or her own medical care at the age of eighteen: http://www.gencourt.state.nh.us/rsa/html/I/21-B/21-B-1.htm

A person who is under the age of 18 years, but who has documentation which supports a claim that he has been emancipated in accordance with the laws of the state in which he previously had been residing, shall be considered to be emancipated in the state of New Hampshire per: http://www.gencourt.state.nh.us/rsa/html/I/21-B/21-B-2.htm

Guardian. A guardian is an individual who is authorized under applicable state or local law to give permission on behalf of a child to general medical care.

Fetus. A fetus means the product of conception from implantation until delivery.

Dead fetus. A fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord.

Delivery. A delivery is a complete separation of the fetus from the woman by expulsion or extraction or any other means.

Neonate. A neonate is a newborn.

Viable. As it pertains to the neonate, viable means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration.

Nonviable neonate. A nonviable neonate means a neonate after delivery that, although living, is not viable.

Pregnancy. A pregnancy encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.

Prisoner. A 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.

12.2 Involvement of Vulnerable Populations

If the IRB reviews research that involves categories of participants vulnerable to coercion or undue influence, the review process should include one or more individuals who are
knowledgeable about or experienced in working with these participants. The IRB may include one or more individuals who are knowledgeable about or experienced in working with individuals from these populations or it may seek such expertise through the use of consultants.

45 CFR 46 has additional subparts designed to provide extra protections for vulnerable populations which also have additional requirements for IRBs.

- 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-conducted or supported research that involves any of these populations must comply with the requirements of the relevant subparts. Research funded by other federal agencies may or may not be covered by the subparts.

In its FWA, Dartmouth limits its commitment to apply Subparts B, C, and D to non-exempt human subjects research conducted or supported by DHHS or any other federal agency that requires compliance with the Subpart(s) (B, C, or D) applicable to the research.

The following policies and procedures, which are based on Subparts B, C, and D, apply to all research regardless of funding. The individual sections describe how the subparts apply specifically to DHHS-funded research.

12.3 Responsibilities

1. The investigator is responsible for identifying the potential for enrolling vulnerable participants in the research proposal, including the possible inclusion of participants who may have impaired decisional capacity, and who are being asked to participate in a research study with greater than minimal risk.

2. The IRB shall include representation, either as members or through the use of consultants, of individual(s) who are knowledgeable about or experienced working with the vulnerable populations involved in the research proposal under review.

3. The IRB reviews the investigator’s justifications for including vulnerable populations in the research to assess appropriateness for inclusion in the research proposal.

4. The IRB must ensure that appropriate additional safeguards have been included in each study to protect the rights and welfare of vulnerable subjects at the time of initial review of the research proposal.

12.4 Procedures

Initial Review of Research Proposal:

1. The investigator identifies the potential to enroll vulnerable participants in the proposed research; provides justification for their inclusion in the study; and describes safeguards
to protect the participant’s rights and welfare. See “Equitable Participant Selection” in application form.

2. The IRB evaluates the proposed safeguards, including the proposed plan for obtaining consent from a legally authorized representative, if applicable, and agreement from vulnerable participants, when possible; determines the need for additional protections and considers, if appropriate, the use of a data and safety monitoring board, consent monitor or participant advocate. See supporting documents “Pregnant women, fetuses, and Neonates” “Children”, and “Individuals with impaired decision making capacity.”

Continuing Review. At Continuing Review the investigator should identify any problems relevant to the rights and welfare of vulnerable population.

12.5 Research Involving Pregnant Women, Human Fetuses and Neonates

According to the Dartmouth FWA, Subpart B of 45 CFR 46 applies only to DHHS-funded research, the funding-source specific requirements are noted in the appropriate sections.

12.5.1 Research Involving Pregnant Women or Fetuses

12.5.1.1 Research Not Conducted or Supported by DHHS

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

Pregnant women or fetuses may be involved in research not funded by DHHS involving more than minimal risk to pregnant women and/or fetuses if all of the following conditions are met:

1. Where 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;

2. 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;

3. Any risk is the least possible for achieving the objectives of the research;

4. If the research holds out the prospect of direct benefit to the pregnant woman, 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 provisions for informed consent;

5. 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.

6. Each individual providing consent under paragraph 4 or 5 of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
7. For children (as defined in Section 12.1) who are pregnant, assent and permission are obtained in accord with the requirements of state law and the IRB;

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

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

10. The IRB may allow individuals whose normal responsibilities include determining the viability of fetuses to be engaged in the research, if their involvement in the determination of viability for an individual fetus cannot be avoided. Confirmation of the determination regarding viability will be sought from a qualified individual who is not otherwise engaged in the research whenever possible prior to beginning the research. The opinion of the independent qualified individual will be documented and made available upon request to the IRB or IRB representative. When advance confirmation is not possible, the investigator will obtain it as soon as s/he can after enrollment, but in all cases within 3 business days. The circumstances that prohibited prospective confirmation of viability and the outcome of the subsequent consultation are reported to the IRB within 5 business days.

12.5.1.2 Research Conducted or Supported by DHHS

For DHHS-conducted or supported research 45 CFR Subpart B applies to all non-exempt human subject research involving pregnant women, fetuses, and neonates.

Pregnant women or fetuses may be involved in research if all of the following conditions are met:

1. Where 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.

2. 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;

3. Any risk is the least possible for achieving the objectives of the research;

4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to 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 accord with the provisions for informed consent.

5. 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.

6. Each individual providing consent under paragraph 4 or 5 of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

7. For children (as defined in Section 12.1) who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent in Section 12.7.2;

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

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

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

12.5.2 Research involving Neonates of Uncertain Viability or Nonviable Neonates

12.5.2.1 Research Not Conducted or Supported by DHHS

Neonates of uncertain viability and nonviable neonates may be involved in research involving more than minimal risk if all of the following conditions are met:

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

2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

3. The IRB may allow individuals whose normal responsibilities include determining the viability of neonates to be engaged in the research, if their involvement in the determination of viability for an individual neonate cannot be avoided. In such cases, confirmation of the determination regarding viability must be made by a qualified individual who is not otherwise engaged in the research whenever possible prior to beginning the research. The opinion of the independent qualified individual will be documented and made available upon request to the IRB or IRB representative. When advance confirmation is not possible, the investigator will obtain it as soon as she/he can after enrollment, but in all cases within 3 business days. The circumstances that prohibited prospective confirmation of viability and the outcome of the subsequent consultation will be reported to the IRB within 5 business days.

4. The requirements for Neonates of Uncertain Viability or Nonviable Neonates (see below in this section) have been met, 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:

The IRB determines that:
1. 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

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

3. 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 provisions of permission and assent, 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 all of the following additional conditions are met:

1. Vital functions of the neonate will not be artificially maintained;
2. The research will not terminate the heartbeat or respiration of the neonate;
3. There will be no added risk to the neonate resulting from the research;
4. The purpose of the research is the development of important knowledge that cannot be obtained by other means; and
5. The legally effective informed consent of both parents of the neonate is obtained in accord with the provisions of permission and assent, except that the waiver and alteration of the provisions of permission and assent 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 the requirements of this paragraph, 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 the requirements of this paragraph.

**12.5.2.2 Research Conducted or Supported by DHHS**

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

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
3. Individuals engaged in the research will have no part in determining the viability of a neonate.

4. The requirements for Neonates of Uncertain Viability or Nonviable Neonates (see below in this section) have been met, 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:

The IRB determines that:

1. 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

2. 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

3. 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 provisions of permission and assent, 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 all of the following additional conditions are met:

1. Vital functions of the neonate will not be artificially maintained;

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

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

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

5. The legally effective informed consent of both parents of the neonate is obtained in accord with the provisions of permission and assent, except that the waiver and alteration of the provisions of permission and assent do not apply.

However, if either parent is unable to consent because of unavailability or incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph, 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 the requirements of this paragraph.
12.5.3 Viable Neonates

After delivery, a viable neonate may be included in research only to the extent permitted by and in accord with the requirements for Research Involving Children (i.e., a viable neonate is a child for purposes of applying federal regulations and Dartmouth policies).

12.5.4 Research Involving, After Delivery, the Placenta, the Dead Fetus or Fetal Material

Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable federal, state, or local laws and regulations regarding such activities.

If information associated with material described above in this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research participants and all pertinent sections of these policies and procedures are applicable.

12.5.5 Research Not Otherwise Approvable

12.5.5.1 Research Not Conducted or Supported by DHHS

If the IRB finds that 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 provisions, then the IRB will consult with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law). Based on the recommendation of the panel, the IRB may approve the research if:

1. The research in fact satisfies the conditions detailed above, as applicable; or
2. All of the following:
   a. 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;
   b. The research will be conducted in accord with sound ethical principles; and
   c. Informed consent will be obtained in accord with the provisions for informed consent and other applicable sections of this manual.

12.5.5.2 Research Conducted or Supported by DHHS

DHHS conducted or supported research that falls in this category must be approved by the Secretary of Health and Human Services. If the IRB finds that 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 provisions, then the research will be sent to OHRP for DHHS review.
12.6 Research Involving Prisoners

The following applies to all research involving prisoners, regardless of funding source. The requirements in this section are consistent with Subpart C of 45 CFR 46, which applies to DHHS-funded or supported research.

12.6.1 Applicability

Dartmouth researchers may engage in research involving prisoners. When applicable the Dartmouth IRBs review research involving prisoners with a properly constituted IRB.

12.6.2 Incarceration of Enrolled Participants

If a participant becomes a prisoner while enrolled in a research study that was not reviewed according to Subpart C, the investigator must promptly notify the IRB and the IRB will:

1. Confirm that the participant meets the definition of a prisoner.

2. Consult with the investigator to determine if it is in the best interests of the participant to continue participation in the study, in part or in full.

3. If the participant should continue, one of two options are available:
   a. Identify an appropriately constituted IRB to review the research, have it reviewed under Subpart C and keep the participant enrolled in the study. If some of the requirements of Subpart C cannot be met or are not applicable (e.g., procedures for the selection of participants within the prison), but it is in the best interests of the participant to remain in the study, keep the participant enrolled and inform OHRP of the decision along with the justification.
   b. Remove the participant from the study and keep the participant on the study intervention under an alternate mechanism such as compassionate use or off label use.

4. If a participant is incarcerated temporarily while enrolled in a study:
   a. If the temporary incarceration has no effect on the study (i.e., there is no need for study activities to take place during the temporary incarceration), keep the participant enrolled.
   b. If the temporary incarceration has an effect on the study, follow the above guidance.

12.7 Research Involving Children

The following applies to all research involving children. 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. The Committee’s receive a laminate handout at each meeting where research involving children will be reviewed for reference.
12.7.1 Allowable Categories

In addition to the IRB’s normal duties, research involving children must be reviewed by the IRB to determine if it fits within and is permissible under one or more federally-defined categories (OHRP/FDA). Each procedure or intervention that the child will undergo for the research must be taken into consideration, and, if the research includes more than one study group assignment (e.g., placebo vs. active, investigational agent vs. comparator) a component analysis must be conducted by the IRB and the category determination must be made for each group assignment. The categories are as follows:

1. **[45 CFR 46.404/21 CFR 50.51] Research/Clinical Investigations not involving greater than minimal risk**  
   Research determined not to involve greater than minimal risk to child participants may be approved by the IRB only if the IRB finds and documents that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians as set forth in Section 12.7.2.

2. **[45 CFR 46.405/21 CFR 50.52] Research/Clinical Investigations involving greater than minimal risk but presenting the prospect of direct benefit to the individual participant**  
   Research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual participant, or by a monitoring procedure that is likely to contribute to the participant’s well-being, may be approved by the IRB only if the IRB finds and documents that:
   - The risk is justified by the anticipated benefit to the participants;
   - The relation of the anticipated benefit to the risk is at least as favorable to the participants as that presented by available alternative options; and
   - Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 12.7.2.

3. **[45 CFR 46.406/21 CFR 50.53] Research/Clinical Investigations involving greater than minimal risk and no prospect of direct benefit to the individual participant, but likely to yield generalizable knowledge about the participant’s disorder or condition.**  
   Research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual participant, or by a monitoring procedure which is not likely to contribute to the well-being of the participant, may be approved by the IRB only if the IRB finds and documents that:
   - The risk represents a minor increase over minimal risk;
   - The intervention or procedure presents experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
• The intervention or procedure is likely to yield generalizable knowledge about the participants’ disorder or condition which is of vital importance for the understanding or amelioration of the disorder or condition; and

• Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 12.7.2.

4. [45 CFR 46.407/21 CFR 50.54] Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children. When the IRB does not believe that the research meets the requirements of any of the above categories, and the IRB finds and documents that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, the IRB shall refer the research for further review as follows:

• HHS conducted or supported research in this category will be referred for review by the Secretary of Health and Human Services. However, before doing so the IRB must determine that the proposed research also meets all of the requirements of the Common Rule.

• FDA-regulated research in this category will be referred for review by the Commissioner of Food and Drugs.

• For research that is not DHHS conducted or supported and not FDA-regulated, the IRB will consult with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law). Based on the recommendation of the panel, the IRB may approve the research if:

  o The research in fact satisfies the conditions of the previous categories, as applicable; or

  o All of the following:

    ▪ The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
    ▪ The research will be conducted in accord with sound ethical principles; and
    ▪ Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 12.7.2.

12.7.2 Parental Permission and Assent

During the meeting, Committee members receive a laminated reference guide when reviewing research involving children.
12.7.2.1 Parental Permission

The IRB must determine that adequate provisions have been made for soliciting the permission of each child’s parent or guardian.

Parents or guardians must be provided with the basic elements of consent and any additional elements the IRB deems necessary, as described in Section 11.5.

The IRB may find that the permission of one parent is sufficient for research to be conducted under Categories 1 [45 CFR 46.404/21 CFR 50.51] & 2 [45 CFR 46.405/21 CFR 50.52] above. The IRB’s determination of whether permission must be obtained from one or both parents will be documented in the reviewer’s notes when a study receives expedited review, and in meeting minutes when reviewed by the convened committee.

Permission from both parents is required for research to be conducted under Categories 3 [45 CFR 46.406/21 CFR 50.53] & 4 [45 CFR 46.407/21 CFR 50.54] above unless

1. One parent is deceased, unknown, incompetent, or not reasonably available; or
2. When only one parent has legal responsibility for the care and custody of the child.

For research not covered by the FDA regulation, the IRB may waive the requirement for obtaining permission from a parent or legal guardian if:

- The research meets the provisions for waiver in Section 11.9 or
- The IRB determines that the research is designed to study conditions in children for which parental or guardian permission is not a reasonable requirement to protect participants (for example, neglected or abused children), provided that an appropriate mechanism for protecting the children who will participate in the research is substituted, and that the waiver is not inconsistent with Federal, State, or local law. The choice of an appropriate mechanism will depend upon the nature and purpose of the activities described in the protocol/research plan, the risks and anticipated benefits to the research participants, and the child’s age, maturity, status, and condition.

Parental permission may not be waived for research covered by the FDA regulations.

Permission from parents or legal guardians must be documented in accordance with and to the extent required by Section 11.6.

12.7.2.2 Assent from Children

The IRB must determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. This judgment may be made for all children to be involved in the study, or for each child, as the IRB deems appropriate. The Committee’s receive a laminated reference guide when reviewing research involving children.

If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that 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 and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the participants are capable of giving assent, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accordance with the applicable regulations. It is important to note that the FDA regulations do permit the IRB to waive the assent requirement if it finds and documents that:

1. The clinical investigation involves no more than minimal risk to the participants;
2. The waiver will not adversely affect the rights and welfare of the participants;
3. The clinical investigation could not practicably be carried out without the waiver; and
4. Whenever appropriate, the participants will be provided with additional pertinent information after participation.

Because “assent” means a child’s affirmative agreement to participate in research, the child must actively show his or her willingness to participate in the research, rather than just complying with directions to participate and not resisting in any way.

The IRB should take into account the nature of the proposed research activity and the age, maturity, and psychological state of the children involved when reviewing the proposed assent procedure and the form and content of the information conveyed to prospective participants. For research activities involving adolescents whose capacity to understand resembles that of adults, the assent procedure should likewise include information similar to what would be provided for informed consent by adults or for parental permission. For children whose age and maturity level limits their ability to fully comprehend the nature of the research activity, but who are still capable of being consulted about participation in research, it may be appropriate to focus on conveying an accurate picture of what the actual experience of participation in research is likely to be (for example, what the experience will be, 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 he or she is capable, what his or her participation in research will involve.

Documentation of Assent

When the IRB determines that assent is required, it also is also responsible for determining whether and how assent must be documented. When the research targets the very young child or children unable or with limited capacity to read or write, an oral presentation accompanied perhaps by some pictures with documentation of assent by the person obtaining assent in a research note is likely more appropriate than providing the child a form to sign. In this case, the investigator should provide the IRB with a proposed script and any materials that they intend to use in explaining the research. See Assent Form template.

When the research targets children who are likely able to read and write, investigators should propose a process and form that is age appropriate and study specific, taking into account the typical child's experience and level of understanding, and composing a document that treats
the child respectfully and conveys the essential information about the study. The assent form should:

1. Tell why the research is being conducted;
2. Describe what will happen and for how long or how often;
3. Say it's up to the child to participate and that it's okay to say no;
4. Explain if it will hurt and if so for how long and how often;
5. Say what the child's other choices are;
6. Describe any good things that might happen;
7. Say whether there is any compensation for participating; and
8. Ask for questions.

Illustrations might be helpful, and larger type and other age appropriate improvements are encouraged when they have the potential to enhance comprehension. Studies involving older children or adolescents should include more information and may use more complex language.

12.7.2.3 Children Who are Wards

Children who are wards of the State or any other agency, institution, or entity can be included in research approved under 45 CFR 46.406/21 CFR 50.53 or 45 CFR 46.407/21 CFR 50.54 (Categories 3 & 4 in Section 12.7.1), only if such research is:

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

If the research meets the condition(s) above, an advocate must be appointed for each child who is a ward (one individual may serve as advocate for more than one child), in addition to any other individual acting on behalf of the child as legal guardian or in loco parentis.

The advocate must 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 and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

The CPHS application asks about the potential for enrolling Wards.

12.8 Adults Lacking Decision Making Capacity

See CPHS Form “Research Involving Individuals Lacking Decision-Making Capacity” for information regarding NH State Law (changed as of January 2015).

Research involving participants who lack the ability to provide consent or who have impaired decision-making capacity should only be conducted when the aims of the research cannot reasonably be achieved without their participation. Participation of this population in research cannot be justified solely on their availability or the convenience for the investigator.
When an investigator seeks to include such participants in research, the investigator must disclose this to the IRB and provide justification for why inclusion is necessary. If capacity to consent is questionable, or may fluctuate, investigators should include provisions for determining capacity to provide informed consent (see Section 11.4), and, if appropriate to reevaluate capacity during participation. When capacity to consent may diminish, the procedures should include, when possible and appropriate, designation of a legally-authorized representative (LAR), inclusion of the LAR in the initial consent discussion and process, and documentation of the participant’s agreement, when possible. When the research includes participants who are likely to regain the capacity to consent, the investigator should include provisions to inform the participant regarding his or her participation and to seek consent for ongoing participation, if applicable.

When the IRB reviews research involving greater than minimal risk and the proposed participant population includes adults who cannot provide consent, may have impaired capacity to provide consent, or whose capacity can be expected to fluctuate over time, the IRB review process will include at least one member, or a consultant, who is experienced with or otherwise knowledgeable about the population.

In evaluating research, the IRB must be able to determine that the risks to participants are reasonable not only in relation to any benefits, but also in relation to the importance of the knowledge that may reasonably be expected to result. In considering the risks of research involving participants who are unable to provide informed consent or who have diminished capacity to do so, the IRB should consider whether any components of the research involve risks that are greater for participants with diminished capacity. For example, the population might experience increased sensitivity or discomfort to certain stimuli or may not be able to verbalize or otherwise demonstrate when they are experiencing discomfort or pain.

As appropriate to the research, the IRB will consider the following in evaluating greater than minimal risk research involving adults unable to consent or lacking decision-making capacity:

1. Whether the aims of the research can reasonably be achieved without inclusion of the population;
2. Whether the research is likely to improve the understanding of the condition, disease, or issue affecting the impaired population;
3. Whether any experimental procedure or intervention has undergone pre-clinical testing or human testing on other populations and whether the data from that testing supports its use in the proposed research;
4. Whether the procedures or interventions that participants will undergo in the research place them at increased risk and if appropriate mechanisms are in place to minimize risks, when possible;
5. Whether the data and safety monitoring plan, including any stopping rules, is appropriate given the risks of the research and the vulnerability of the population;
6. Whether the procedures for withdrawing an individual participant from the research are appropriate;
7. Whether the recruitment procedures, consent process, and plans for financial compensation support voluntariness and minimize the likelihood of undue influence or coercion;

8. Whether participants will be exposed to financial or other risks that they might not consider acceptable if they had the capacity to provide consent, and whether appropriate mechanisms have been put into place to minimize these risks;

9. Whether procedures for determining capacity to provide consent, and for evaluating capacity on an ongoing basis, if applicable, are appropriate;

10. Whether the procedures for informing participants who regain capacity about their involvement in the research, and for obtaining consent for on-going participation, if applicable, are appropriate;

11. Whether assent should be required when possible, and, if so, if the proposed procedures to obtain and document assent are appropriate;

12. Whether a research participant advocate or consent monitor should be required for some or all participants.

13. **FDA-Regulated Research**

FDA regulations apply to research that involves a FDA-regulated test article in a clinical investigation involving human subjects as defined by the FDA regulations. For FDA-regulated research, the IRB must apply the FDA regulations at 21 CFR 50 and 21 CFR 56.

Clinical trials with investigational drugs must be conducted according to FDA’s IND regulations, 21 CFR Part 312, and other applicable FDA regulations. Use of an investigational device in a clinical trial to obtain safety and effectiveness data must be conducted according to FDA’s IDE regulations, 21 CFR Part 812, and other applicable FDA regulations.

The Clinical Trials Office (CTO) is responsible for the oversight of FDA-regulated clinical trials. All Clinical Trial Agreements (CTAs) have language indicating all parties will abide by applicable laws and regulations governing clinical research. Including, Sec. 312.50 General responsibilities of sponsors: "...ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug." And Sec. 312.55 Informing investigators. "(b) The sponsor shall, as the overall investigation proceeds, keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use."

13.1 **Definitions**

**Biologic.** Biological products include a wide range of products such as vaccines, blood and blood components, allergens, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources — human, animal, or microorganism — and may
be produced by biotechnology methods and other technologies. In general, the term "drugs" includes therapeutic biological products.

**Dietary Supplement.** A dietary supplement is a product taken by mouth that is intended to supplement the diet and that contains a dietary ingredient. The dietary ingredients in these products can include vitamins, minerals, herbs and other botanicals, amino acids, other dietary substances intended to supplement the diet, and concentrates, metabolites, constituents, extracts, or combinations of the preceding types of ingredients. See section 201(ff) of the FD&C Act [21 U.S.C. 321(ff)].

**Investigational Drug.** *Investigational or experimental* drugs are new drugs that have not yet been approved by the FDA or approved drugs that are being studied in a clinical investigation.

**Investigational Device.** Investigational device means a device (including a transitional device) that is the object of an investigation. Investigation, as it pertains to devices, means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.

**IND.** IND means an investigational new drug application in accordance with 21 CFR Part 312.

**IDE.** IDE means an investigational device exemption in accordance with 21 CFR 812.

**In Vitro Diagnostic Product (IVD).** In vitro diagnostic products are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. [21 CFR 809.3(a)]

**Emergency Use.** Emergency use is defined as the use of an investigational product with a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval. [21CFR 56.102(d)]

**Significant Risk (SR) Device.** Significant risk device means an investigational 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 device that does not meet the definition of a significant risk device.
Humanitarian Use Device (HUD). A Humanitarian Use Device is a device intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year.

13.2 FDA Exemptions

The following categories of clinical investigations are exempt from the requirements of FDA regulations for IRB review:

1. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review. [21 CFR §56.104(c)]

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)]

13.3 Procedures

A. At initial submission, the investigator indicates whether the research involves a test article and is a clinical investigation involving human participants on the application form.

B. During the pre-review process, the IRB Office staff confirms whether FDA regulations are applicable

C. If the study involves investigational drugs and is industry sponsored and the sponsor requires ICH-GCP E6 compliance, that requirement is identified in the CTA negotiated with the institution and in the protocol. The Clinical Trials Office is responsible for ensuring compliance and confirmation with the investigator. Dartmouth follows ICH-GCP E6 to the extent it is consistent with FDA regulations.

13.4 Investigator Responsibilities

The investigator holds additional responsibilities when conducting a clinical trial evaluating FDA-regulated drugs, devices, and other articles. These responsibilities include, but are not limited to, the following:

1. The investigator is responsible for ensuring that a clinical investigation is conducted according to the signed investigator statement for clinical investigations of drugs (including biological products) or agreement for clinical investigations of medical devices, the investigational plan and other applicable regulations, and any requirements imposed by the IRB or FDA.
2. The investigator is responsible for personally conducting or supervising the investigation. When certain study-related tasks are delegated by an investigator, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

3. The investigator must maintain a list of the appropriately qualified persons to whom significant trial-related duties have been delegated. This list should also describe the delegated tasks, identify the training that individuals have received that qualifies them to perform delegated tasks (e.g., it can refer to an individual’s CV on file and/or training conducted by the investigator/sponsor), and identify the dates of involvement in the study. An investigator should maintain separate lists for each study conducted by the investigator.

4. The investigator is responsible for protecting the rights, safety, and welfare of subjects under their care during a clinical trial. This responsibility includes:
   - Informing subjects that the test article is being used for investigational purposes and ensuring that the requirements relating to obtaining informed consent are met
   - Providing reasonable medical care for study subjects for medical problems arising during participation in the trial that are, or could be, related to the study intervention
   - Providing reasonable access to needed medical care, either by the investigator or by another identified, qualified individual (e.g., when the investigator is unavailable, or when specialized care is needed)
   - Adhering to the protocol/research plan so that study participants are not exposed to unreasonable risks
   - Informing the participant’s primary physician about the participant’s participation in the study if the participant has a primary physician and the participant agrees to the primary physician being informed

5. The investigator is responsible for reading and understanding the information in the investigator brochure or device risk information, including the potential risks and side effects of the drug or device.

6. The investigator is responsible for maintaining adequate and accurate records in accordance with FDA regulations and to making those records available for inspection by the FDA. These records include: correspondence with other investigators, the IRB, the sponsor, monitors, or the FDA; drug and device accountability records; case histories; consent forms; and documentation that consent was obtained prior to any participation in the study. Records are retained indefinitely in an electronic format. If other regulations, such as HIPAA, organizational policies, or contractual agreements with sponsors require retention in a different format for a specified period of time that requirement is followed.
7. The investigator is responsible for controlling drugs, biological products, and devices according to FDA regulations and the Controlled Substances Act, if applicable.

8. The investigator proposing the clinical investigation is required to provide a plan – to be evaluated by the appropriate component of the HRPP - that includes storage, security, and dispensing of the test article.

   a. The investigator is responsible for investigational drug accountability that includes storage, security, dispensing, administration, return, disposition, and records of accountability. All drugs received for a study must be stored in a locked environment under secure control with limited access. A log must be kept regarding the receipt, use, and/or dispensing of the device and the disposition of remaining devices at the conclusion of the investigation.

   b. All devices received for a study must be stored in a locked environment under secure control with limited access. Proper instructions on the use of the device must be provided to study participants, where appropriate. A log must be kept regarding the receipt, use, and/or dispensing of the device and the disposition of remaining devices at the conclusion of the investigation.

9. All reports required by the sponsor to be submitted to the IRB shall be submitted.

10. The investigator will permit inspection of research records by the sponsor, sponsor representatives, the FDA, OHRP, accrediting bodies, Dartmouth IRB, Clinical Trials Office, Office of Sponsored Programs, and Office of Research Compliance representatives and any other agencies or individuals entitled to inspect such records under regulation, organizational policy, or contractual agreement.

13.5 Dietary Supplements

Research involving dietary supplements may or may not fall under FDA regulations. Under the Dietary Supplement Health and Education Act (DSHEA) of 1994, a dietary supplement is not considered a drug and is not subject to the premarket approval requirements for drugs if the intended use for which it is marketed is only to affect the structure or any function of the body (i.e., not intended to be used for a therapeutic purpose). Whether a study falls under FDA oversight is determined by the intent of the clinical investigation. If the clinical investigation is intended only to evaluate the dietary supplement’s effect on the structure or function of the body, FDA regulations do not apply. If the study is intended to evaluate the dietary supplement’s ability to diagnose, cure, mitigate, treat, or prevent a disease, then FDA regulations apply. Studies involving the ingestion of dietary supplements that are not subject to FDA oversight are still research, and must be reviewed by the IRB.

Whether an IND is needed for a study evaluating a dietary supplement is determined by the intent of the study. If the study is intended only to evaluate the dietary supplement’s effect on the structure or function of the body, an IND is not required. If the study is intended to evaluate the dietary supplement’s ability to diagnose, cure, mitigate, treat, or prevent a disease, an IND is required under part 312.
The investigator must supply the IRB with sufficient information to determine that the criteria for approval are satisfied and to determine or verify whether or not the research requires an IND. Applications should provide detail consistent with that expected on a drug protocol/research plan and consistent with the level of risk associated or anticipated with the research. At a minimum, the research plan should provide the following information regarding the supplement: Name, Manufacturer, Formulation, Dosage, Method/Route of Administration, Mechanism of Action, Known Drug Interactions, Risk Profile, IND number (or justification for why an IND is unnecessary), documentation of approval for use in humans, documentation or certification of Quality or Purity and an accountability plan for the product describing where it will be stored and how it will be dispensed, usage tracked and final disposition, disposal or return. If the study entails greater than minimal risk, a plan for Data and Safety Monitoring must be included.

13.6 Clinical Investigations of Drugs and Devices

13.6.1 IND/IDE Requirements

For studies evaluating the safety or effectiveness of medical devices or experiments using drugs, biologics, dietary supplements, and other compounds that may be considered a drug under FDA regulations, the investigator must indicate on the IRB application whether or not an IDE or IND is in place, and, if not, the basis for why an IDE or IND is not needed. Documentation of the IND/IDE must be provided by the sponsor or the sponsor-investigator. Documentation of the IND/IDE could be a:

1. Industry sponsored study with IND/IDE number indicated on the protocol/research plan.
2. Letter/communication from FDA.
3. Letter/communication from industry sponsor.
4. Other document and/or communication verifying the IND/IDE.

For investigational devices, the study may be exempt from IDE requirements or, in the case of Non-significant Risk (NSR) device studies, follow abbreviated IDE requirements which do not require formal approval by the FDA. If the sponsor has identified a device study as exempt or NSR, then the investigator should include documentation with the submission providing the basis for exempt or NSR categorization. If the FDA has determined that the study is exempt or NSR, documentation of that determination must be provided.

The IRB reviews the application and, based upon the documentation provided, determine: (1) that there is an approved IND/IDE in place, (2) that the FDA has determined that an IND is not required or that a device study is exempt or NSR, or, (3) whether or not an IND is necessary, or that a device study is exempt or NSR, using the criteria below. The IRB cannot grant approval and research cannot begin, including recruiting, obtaining consent, and screening participants to the research until the IND/IDE status is determined, and, if necessary, an approved IND or IDE is in place. Please Note: An IND goes into effect 30 days after the FDA receives the IND, unless the sponsor receives earlier notice from the FDA.
13.6.1.1 IND Exemptions

For drugs, an IND is not necessary if the research falls in one of the following seven (7) categories:

1. The drug being used in the research is lawfully marketed in the United States and all of the following requirements are met:
   a. The research is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug
   b. In the case of a prescription drug, the research is not intended to support a significant change in the advertising for the product;
   c. The research does not involve a route of administration, dose, subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
   d. The research is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];
   e. The research is conducted in compliance with the requirements of 21 CFR 312.7 (i.e., the research is not intended to promote or commercialize the drug product); and
   f. The research does not intend to invoke FDA regulations for planned emergency research [21 CFR 50.24].
2. The research only involves one or more of the following: (a) Blood grouping serum, (b) Reagent red blood cells or (c) Anti-human globulin;
3. For clinical investigations involving an in vitro diagnostic biological product, an IND is not necessary if a) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and b) it is shipped in compliance with 21 CFR 312.160
4. A clinical investigation involving use of a placebo is exempt from FDA requirements if the investigation does not otherwise require submission of an IND.
5. Bioavailability or Bioequivalence (BA/BE) studies if all of the following conditions are met:
   a. The drug product does not contain a new chemical entity [21 CFR 314.108], is not radioactively labeled, and is not cytotoxic;
   b. The dose (single dose or total daily dose) does not exceed the dose specified in the labeling of the approved version of the drug product;
   c. The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively]; and
   d. The sponsor meets the requirements for retention of test article samples [21 CFR 320.31(d)(1)] and safety reporting [21 CFR 320.31(d)(3)].
6. Research using a radioactive drug or biological product if all of the following conditions are met:

118
a. It involves basic research not intended for immediate therapeutic, diagnostic, or similar purposes, or otherwise to determine the safety and efficacy of the product;
b. The use in humans is approved by a Radioactive Drug Research Committee (RDRC) that is composed and approved by FDA;
c. The dose to be administered is known not to cause any clinically detectable pharmacological effect in humans; and
d. The total amount of radiation to be administered as part of the study is the smallest radiation dose practical to perform the study without jeopardizing the benefits of the study and is within specified limits.

7. FDA practices enforcement discretion for research using cold isotopes of unapproved drugs if all of the following conditions are met:
   a. The research is intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a drug labeled with a cold isotope or regarding human physiology, pathophysiology, or biochemistry;
   b. The research is not intended for immediate therapeutic, diagnostic, or preventive benefit to the study subject;
   c. The dose to be administered is known not to cause any clinically detectable pharmacologic effect in humans based on clinical data from published literature or other valid human studies;
   d. The quality of the cold isotope meets relevant quality standards; and
   e. The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively].

13.6.1.2 IDE Exemptions

For clinical investigations of devices, an IDE is not necessary if:

1. The research involves a 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;

2. The research involves a device other than a transitional device, introduced into commercial distribution on or after May 28, 1976, 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 (a “501k” device);

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

4. 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;

5. The research involves a device intended solely for veterinary use;

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

7. 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.

13.6.1.3 Significant and Non-Significant Risk Device Studies

A device study is a Non-Significant Risk (NSR) Device study if it is not IDE exempt and does not meet the definition of a Significant Risk (SR) Device study.

Under 21 CFR 812.3(m), an SR device means an investigational device that:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- 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
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

If the FDA has already determined a study to be SR or NSR, documentation evidencing such should be provided to the IRB as described in Section 13.6.1. The FDA’s determination is final and the IRB does not have to make the device risk determination.

If the FDA has not already made a device risk determination for the study and the sponsor or investigator declares the device risk to be NSR, the IRB reviews the study at a convened meeting to determine if the device represents SR or NSR.

The sponsor or sponsor-investigator is responsible for providing the IRB with an explanation describing the basis for the initial determination of NSR and any other information that may help the IRB in evaluating the risk of the study (e.g., reports of prior investigations of the device). The IRB reviews the explanation and other information provided, including, but not limited to: a description of the device, reports of prior investigations of the device (if applicable), the proposed investigational plan, and participant selection criteria.
The NSR/SR determination made by the IRB is based on the proposed use of the device in the investigation, not on the device alone. The IRB considers the nature of any harms that may result from use of the device, including potential harms from additional procedures participants undergo as part of the investigation (e.g., procedures for inserting, implanting, or deploying the device). The IRB may consult with the FDA or require the sponsor or investigator to obtain a determination from the FDA. The IRB documents the SR or NSR determination in the electronic protocol records and the basis for it in the meeting minutes and provides the investigator, and sponsor when applicable, with the determination in writing.

Non-significant risk device studies do not require submission of an IDE application to the FDA but must be conducted in accordance with the abbreviated requirements of IDE regulations (21 CFR 812.2(b)). Under the abbreviated requirements, the following categories of investigations are considered to have approved applications for IDE’s, unless FDA has notified a sponsor under 812.20(a) that approval of an application is required:

1. An investigation of a device other than a significant risk device, if the device is not a banned device and the sponsor (or sponsor-investigator):
   (i) Labels the device in accordance with 812.5;
   (ii) Obtains IRB approval of the investigation after presenting the reviewing IRB with an explanation of why the device is not a significant risk device, and maintains such approval;
   (iii) Ensures that each investigator participating in an investigation of the device obtains from each participant under the investigator’s care, informed consent under 21 CFR Part 50 and documents it, unless documentation is waived by an IRB under 56.109(c).
   (iv) Complies with the requirements of 812.46 with respect to monitoring investigations;
   (v) Maintains the records required under 812.140(b) (4) and (5) and makes the reports required under 812.150(b) (1) through (3) and (5) through (10);
   (vi) Ensures that participating investigators maintain the records required by 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7); and
   (vii) Complies with the prohibitions in 812.7 against promotion and other practices.

When the FDA or IRB determines that a study is SR the IRB does not approve the study until an IDE is obtained.

13.7 Humanitarian Use Devices

A Humanitarian Use Device (HUD) is an approved (marketed) medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year [21 CFR 814.3(n)].
Federal law requires that IRBs approve the use of an HUD at a facility. Once approved, the clinical use of the HUD may be considered as any other approved device, with the caution that effectiveness has not been shown in clinical trials.

13.7.1 Definitions

Humanitarian Device Exemption: A Humanitarian Device Exemption (HDE) is a “premarket approval application” submitted to FDA pursuant to Subpart A, 21 CFR Part 814 “seeking a humanitarian device exemption from the effectiveness requirements of sections 514 and 515 of the [FD&C Act] as authorized by section 520(m)(2) of the [FD&C Act].” HDE approval is based upon, among other criteria, a determination by FDA that the HUD does not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from use of the device outweighs the risk of injury or illness from its use while taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

HDE Holder: The HDE Holder is a person who, or entity that, obtains approval of an HDE from the FDA.

13.7.2 IRB Review Requirements

A Humanitarian Use Device (HUD) may only be used after the IRB has approved its use, except in certain emergencies. The HDE holder is responsible for ensuring that a HUD is provided only to facilities having an IRB constituted and acting in accordance with the FDA’s regulations governing IRBs (21 CFR Part 56), including continuing review of use of the device.

When a HUD is used in a clinical investigation (i.e., research involving one or more participants to determine the safety or effectiveness of the HUD), the full requirements for IRB review and informed consent apply (21 CFR 50 and 56), as well as other applicable regulations. It is essential to differentiate whether the HUD is being studied for the indication(s) in its approved labeling or for different indication(s). When the HUD is being studied for the indication(s) in its approved labeling, the IDE regulations at 21 CFR 812 do not apply. However, when the HUD is being studied for a different indication(s), 21 CFR 812 applies, including the requirement for a FDA-approved IDE before starting the clinical investigation of a Significant Risk device.

13.7.3 Procedures

The relevant requirements and procedures for investigators and for IRB review described elsewhere in this manual apply to clinical investigations of HUDs. The material within this section applies to diagnostic or treatment uses of HUDs.

The health care provider seeking approval for diagnostic or treatment use of a HUD at Dartmouth is responsible for obtaining IRB approval prior to use of the HUD at Dartmouth and for complying with the applicable regulations, including those for medical device reporting, institutional policies, and the requirements of the IRB.
Health care providers seeking initial IRB approval for diagnostic or treatment use of a HUD for the indication(s) in the HUDs approved labeling should submit the following materials to the IRB:

1. IRB application
2. A copy of the HDE approval letter from the FDA
3. A description of the device, such as a device brochure
4. The patient information packet for the HUD
5. The proposed clinical consent process and document.
6. Other relevant materials as identified in the IRB application

The IRB reviews the proposal at a convened meeting ensuring that appropriate expertise is available either within the membership in attendance or via the use of consultants. The IRB reviews the risks to patients that are described in the product labeling and other materials, the proposed procedures to ensure that risks are minimized, and evaluates whether the risks are reasonable in relation to the potential benefits to patients at the facility. The IRB evaluates the patient information packet and proposed consent process and determines if the materials are adequate and appropriate for the patient population.

The IRB may specify limitations on the use of the device, require additional screening and follow up procedures, require interim reports to the IRB, require continuing review more often than annually, or set other conditions or requirements as appropriate to minimize risks to patients and ensure the safe use of the device in the facility.

Once use of the HUD is approved, the health care provider is responsible for submitting any proposed changes to the IRB-approved plan or patient materials and obtaining approval for those changes prior to implementation, unless the change is necessary to avoid or mediate an apparent immediate risk to a patient. Proposed changes are submitted with a Request for Modification and accompanied by any revised materials or supporting documentation. The IRB may review these changes using expedited review procedures or refer the changes for review by the convened IRB.

The health care provider is responsible for submitting reports to the FDA, the IRB, and the manufacturer/HDE Holder whenever a HUD may have caused or contributed to a death, and must submit reports to the manufacturer (or to FDA and the IRB if the manufacturer is unknown) whenever a HUD may have caused or contributed to a serious injury (21 CFR 803.30 and 814.126(a)). Serious injury means an injury or illness that (1) is life-threatening, (2) results in permanent impairment of a bodily function or permanent damage to a body structure, or (3) necessitates medical or surgical intervention to preclude permanent impairment of a bodily function or permanent damage to a body structure (21 CFR 803.3). The specific requirements for this reporting are in the Medical Device Reporting (MDR) Regulation, at 21 CFR Part 803. The IRB reviews these reports via either expedited or convened review, as appropriate, and considers whether any changes are needed to the IRB-approved plan or patient materials.

The health care provider is responsible for submitting continuing review materials to the IRB.
sufficiently in advance of the expiration date to ensure IRB review and re-approval prior to expiration. Materials to be submitted include:

1. The Continuing Review Form
2. Any safety reports or summaries provided by the HDE holder that had not previously been submitted
3. Other materials as identified on the Continuing Review Report
4. Any other new relevant information or materials

The IRB may conduct continuing review using expedited review procedures or review by the convened IRB.

13.7.4 Emergency Uses of HUDs

If an appropriately trained and licensed health care provider in an emergency situation determines that IRB approval for the use of the HUD at the facility cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be used without prior IRB approval. The health care provider must provide written notification of the use to the IRB, within 5 working days after the emergency use of the device, including the identification of the patient involved, the date of the use, and the reason for the use.

If a HUD is approved for use in a facility, but an appropriately trained and licensed health care provider wants to use the HUD outside its approved indication(s) in an emergency or determines that there is no alternative device for a patient’s condition, the physician should consult with the HDE holder and IRB in advance if possible, obtain informed consent if possible, and ensure that reasonable measures are taken to protect the well-being of the patient such as a schedule and plan for follow up examinations and procedures to monitor the patient, taking into consideration the patient’s specific needs and what is known about the risks and benefits of the device. The provider should submit a follow up report to the HDE holder and the IRB and must comply with medical device reporting requirements.

The IRB may require additional reports, patient protection measures, or other requirements, as appropriate given the specifics of the situation.

13.8 Expanded Access to Investigational Drugs, Biologics, and Devices

Expanded access pathways, also referred to as “compassionate use”, are designed to make investigational medical products available as early in the drug and device evaluation process as possible to patients without therapeutic options, because they have exhausted or are not a good candidate for approved therapies and cannot enter a clinical trial. Expanded access refers to access to investigational medical products outside of a clinical trial, where the intent is treatment, rather than research. Because the investigational products have not yet been approved by FDA as safe and effective, it is important to remember that the product may not be effective and there may be unexpected serious adverse effects and to take appropriate measures to ensure that this is understood by the patient or their representative and to monitor for safety.
13.8.1 Expanded Access to Investigational Drugs and Biologics

The FDA’s expanded access rule for investigational drugs, including biologics classified as drugs, is intended to improve access to investigational drugs, and approved drugs with limited availability under a risk evaluation and mitigation strategy (REMS), for patients with serious or immediately life-threatening diseases or conditions who lack other therapeutic options and may benefit from the investigational diagnostic or therapy.

Under the FDA’s expanded access rule, access to investigational drugs for treatment purposes is available to:

- Individual patients, including in emergencies [21 CFR 312.310]
- Intermediate-size patient populations [21 CFR 312.315]
- Larger populations under a treatment protocol or treatment IND [21 CFR 312.320]

Expanded access submissions are categorized by FDA as either “Access Protocols”, which involve a protocol amendment to an existing IND, or “Access INDs”, which are managed separately from any existing INDs.

The FDA has also established a rule, “Charging for Investigational Drugs Under an Investigational New Drug Application”, to:

- Provide general criteria for authorizing charging for an investigational drug [21 CFR 312.8(a)]
- Provide criteria for charging for an investigational drug in a clinical trial [21 CFR 312.8(b)]
- Set forth criteria for charging for an investigational drug under the expanded access for treatment use
- Clarify what costs can be recovered

Investigators, when seeking access to drugs under the expanded access provisions, should work closely with the sponsor or manufacturer, the FDA, and the Dartmouth IRB Office, to determine the appropriate access mechanism and ensure that proper regulatory procedures are followed.

Unless the conditions that permit an emergency use exemption (See Section 13.9) are satisfied, prospective IRB review and approval is required for all expanded access uses, including clinical patient use. This requires, among other things, that the IRB review the expanded access use at a convened meeting at which a majority of IRB members are present.

13.8.2 Expanded Access to Investigational and Unapproved Medical Devices

As with investigational drugs, unapproved medical devices may normally only be used in humans in an approved clinical trial under the supervision of a participating clinical investigator. However, there may be circumstances under which a health care provider may wish to use an unapproved device when a patient is facing life-threatening circumstances or suffering from a
serious disease or condition for which no other alternative therapy or diagnostic exists or is a satisfactory option for the patient.

FDA has made the following mechanisms available for these circumstances:

- Emergency Use
- Planned Emergency Research (See Section 11.11.1)
- Compassionate Use (or Single Patient/Small Group Access)
- Treatment Use
- Continued Access

Investigators, when seeking access to investigational or unapproved devices under one of the above provisions, should work closely with the sponsor or manufacturer, the FDA, and the Dartmouth IRB Office to ensure that proper regulatory procedures are followed.

Unless the conditions that permit an emergency use exemption are satisfied (See Section 13.9), prospective IRB review at a convened meeting and approval is required.

13.9 Emergency Use

If an appropriately trained and licensed health care provider in an emergency situation determines that IRB approval for the use of an investigational drug/device at the facility cannot be obtained in time to prevent serious harm or death to a patient, the drug or device may be used without prior IRB approval. The health care provider must provide written notification of the use to the IRB within 5 working days after the emergency use of the drug or device including the identification of the patient involved, the date of the use, and the reason for the use.

Note: DHHS regulations do not permit research activities to be started, even in an emergency, without prior IRB approval. When emergency medical care is initiated without prior IRB review and approval, the patient may not be considered a research participant under 45 CFR Part 46. However, nothing in the DHHS regulations at 45 CFR Part 46 is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state or local law.

13.9.1 Emergency Exemption from Prospective IRB Approval

Under FDA regulations [21 CFR 56.104(c)], FDA exempts the emergency use of a test article from the requirement for prospective IRB approval, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article in the facility requires IRB review. However, FDA acknowledges that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.
FDA defines emergency use as the use of a test article in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval [21 CFR 56.102(d)]. If all conditions described in 21 CFR 56.102(d) exist then the emergency exemption from prospective IRB approval found at 21 CFR 56.104(c) may be used. The emergency use of a test article, other than a medical device, is a clinical investigation, the patient is a participant, and the FDA may require data from an emergency use to be reported in a marketing application.

Life-threatening, for the purposes of 21 CFR 56.102(d), includes both life-threatening and severely debilitating.

Unless the provisions for an emergency exception from the informed consent requirement are satisfied (See Section 13.9.2), informed consent must be obtained in accordance with 21 CFR 50 and documented in writing in accordance with 21 CFR 50.27.

The IRB Chair or designated member reviews the report to verify that circumstances of the emergency use conformed to FDA regulations. This review is not approval for the emergency use by the IRB, as an exemption from the requirement for prospective IRB approval has been invoked. When appropriate, in the event a manufacturer requires documentation from the IRB, the IRB provides a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of 21 CFR 56.104(c). Emergency Use reports are brought to the convened IRB for its information.

Investigators must comply with all other organizational policies and requirements applicable to the use of the investigational or unapproved article.

13.9.2 Emergency Exception from the Informed Consent Requirement

An exception under FDA regulations at 21 CFR 50.23(a-c) permits the emergency use of an investigational or unapproved test article without informed consent where the treating physician and an independent physician who is not otherwise participating in the clinical care certify in writing all four of the following specific conditions:

a. The patient 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 patient;

c. Time is not sufficient to obtain consent from the patient’s LAR; and

d. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the life of the patient.

If immediate use of the test article is, in the treating physician’s opinion, required to preserve the life of the patient, and time is not sufficient to obtain the independent physician determination in advance of using the test article, within 5 working days after the use of the article, the determinations of the treating physician shall be reviewed and evaluated in writing by a physician who is not participating in the clinical care.

127
The IRB must be notified within 5 working days when an emergency exception is used. The IRB Chair or designated member reviews the report to verify that circumstances of the emergency exception conformed to FDA regulations and reports such use to the convened IRB.

13.9.3 **Waiver of Informed Consent for Planned Emergency Research**

Dartmouth IRB follows FDA regulations, 21 CFR 50.24, and any applicable state requirements which permit waiver of informed consent requirements for emergency research when human research participants in need of emergency medical intervention cannot provide legally effective informed consent and their LAR is also unable or unavailable to give informed consent on the participant’s behalf.

See Section 11.11.1 for additional detail on Planned Emergency Research.

14 **Reportable Events**

Regulations require an organization to have written procedures for ensuring prompt reporting of changes in research activity; unanticipated problems involving risk to participants or others; and any instances of serious or continuing non-compliance to the IRB, organizational officials, and applicable federal agencies. In order to comply with this requirement, Dartmouth has procedures to review issues that arise during the conduct of research.

The following section provides definitions and procedures regarding issues that arise during the conduct of research that must be reported to the IRB.

14.1 **Definitions**

**Unanticipated problems involving risk to participants or others:** Unanticipated problems involving risks to participants or others (UPs) refer to any incident, experience, outcome, or new information that:

1. Is unexpected
2. Is related or possibly related to participation in the research, and
3. Indicates that participants or others are at a greater risk of harm (including physical, psychological, economic, legal or social harm) than was previously known or recognized.

**Unexpected:** The incident, experience or outcome is not expected (in terms of nature, severity, or frequency) given the research procedures that are described in the study-related documents, such as the IRB-approved research protocol/research plan and informed consent documents; and the characteristics of the population being studied.

**Related:** There is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.

**Adverse Event:** For the purposes of these policies and procedures, an adverse event (AE) is any untoward or unfavorable occurrence in a human research participant, including any abnormal
sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant’s participation in the research, whether or not considered related to participation in the research. Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.

**Unanticipated Adverse Device Effect:** An Unanticipated Adverse Device Effect (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that related to the rights, safety, or welfare of research participants [21 CFR 812.3(s)].

**Protocol/Research Plan Deviations:** A protocol/research plan deviation is defined as a variation from the IRB approved research plan that happens without prior review and approval of the IRB (e.g., study visit outside protocol/research plan window, blood work drawn outside protocol/research plan window, etc.). Depending on the details, protocol/research plan deviations may be determined to be non-compliance (serious, continuing, or otherwise).

**Protocol/Research Plan Exceptions:** Protocol/research plan exceptions are planned deviations from the protocol/research plan. Exceptions are anticipated and must occur with prior agreement from the sponsor, if applicable, and approval by the IRB. If an exception is implemented without IRB approval, it is a deviation, even when the sponsor has approved.

### 14.2 Procedures

#### 14.2.1 Reporting

Adverse events in clinical trials must be reported to the sponsor in compliance with FDA regulations and sponsor requirements. Unless specifically required by the IRB, the Dartmouth IRB does not accept reports of adverse events and IND Safety Reports that do not meet the definition of an unanticipated problem involving risks to participants or others.

Investigators must report the following events or issues to the IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event:

1. Changes made to the research without prior IRB approval to eliminate apparent immediate hazards to the participant(s);

2. Adverse events (either local or external) involving direct harm to participants enrolled by the investigator (i.e., local adverse events), which in the opinion of the investigator or sponsor, may represent an unanticipated problem involving risk to participants or others;

3. An unanticipated event related to the research that exposes participants to potential risk but that does not involve direct harm to participants;
4. An unanticipated event related to the research that results in actual harm or exposes individuals other than the research participants (e.g., investigators, research assistants, students, the public, etc.) to potential risk;

5. IND Safety Reports from sponsors that meet the criteria for an unanticipated problem involving risk to participants;

6. New information that indicates an increase to the risks or decrease to potential benefits of the research;

7. New information that may impact the willingness of participants to continue in the research;

8. A breach of confidentiality;

9. Incarceration of a participant in a study not approved to enroll prisoners;

10. Complaint of a participant when the complaint involves the health, safety, or rights of the participant or indicates unexpected risks, possible non-compliance, or cannot be resolved by the research team;

11. Protocol/research plan deviations, with the exception of minor deviations. Minor deviations (deviations that do not impact participant safety, compromise the integrity of study data and/or affect the participant’s willingness to participate in the research) are to be reported at the time of continuing review.

12. Sponsor or lead investigator/coordinating center imposed suspension or termination of some or all research activities;

13. Unanticipated adverse device effects (UADEs) (Note: Regulations require that UADEs be reported to the sponsor and IRB as soon as possible but in no event later than 10 working days after the investigator first learn of the event [21 CFR 812.150(a)(1)].)

14. Any other event that indicates participants or others might be at risk of serious, unanticipated harms that are reasonably related to the research.

**14.2.2 Submission of Reports**

Investigators or the study team must report possible problems or issues with the research to the IRB Office via the Rapport management system. The written report should contain the following as applicable:

a. Detailed information about the event or issue, including relevant dates;

b. Any corrective and preventative actions, planned or already taken, to ensure that the issue or problem is corrected and will not occur again;

c. An assessment of whether any participants or others were placed at risk as a result of the event or suffered any harm (e.g., physical, social, financial, legal or psychological) and any plan to address these consequences;

d. If a report from a sponsor is the basis for the report of a possible unanticipated problem involving risks to participants or others, or a sponsor has requested the
submission to the IRB, the report should be accompanied by an analysis from the sponsor detailing (1) how the event or problem meets the definition of a UP; (2) proposed study-wide corrective actions or modifications to the research along with a timeline for anticipated completion of the actions; and (3) whether or not the problem has been reported as a UP to any relevant federal agencies;

e. If a sponsor, lead investigator or coordinating center suspends or terminates some or all research activities, the report should be accompanied by information from the sponsor detailing (1) why the suspension or termination was enacted; (2) if it was due to a possible UP (in which case the information in “d” above must be included); (3) any impact on participants or others and actions to be taken to protect participants; (4) any plan to inform participants of the suspension or termination and other pertinent information; and (5) whether the suspension or termination has been reported to any relevant federal agencies;

f. Other relevant information;

Reports are screened by the IRB Office staff and immediately forwarded to the IRB Director, Chair, or designee if the IRB Office staff believes that immediate intervention may be required to protect participants or others from serious harm.

14.2.3 IRB Procedures for Handling Reportable Events

1. Upon receipt of a report of an event from an investigator, the IRB staff checks for completeness. If any applicable information (as detailed above) is missing or incomplete, the IRB staff contacts the investigator or the designated contact person to obtain additional information.

2. The IRB Chair and/or other experienced member(s) designated by the IRB Chair receives and reviews the report. The reviewer(s) make the initial determination as to whether the event is as an unanticipated problem and/or non-compliance (See Section 15 for procedures for unanticipated problems, and Section 16 for serious or continuing non-compliance).

3. Based on the information received from the investigator, the IRB Chair or designee may suspend the research to ensure protection of the rights and welfare of participants. Suspension directives made by the IRB Chair or designee are reported to a meeting of the convened IRB and follow Dartmouth notification procedures for IRB suspensions.

4. The IRB or the IRB Chair (or designee) has the authority to require submission of more detailed information from the investigator, the sponsor, the study coordinating center, or DSMB/DMC about any event occurring in a research study as a condition of the continuation of the IRB’s approval of the research.

5. If the IRB Chair or designee determines that the problem reported does not meet the definition of an unanticipated problem or serious or continuing non-compliance, the reviewer considers whether any corrective or preventative actions planned or already taken are sufficient and whether modifications to the research plan, consent document,
or corrective action plan may be necessary, and refer the matter to the convened IRB for review, if appropriate. The results of the review are recorded in the study record and communicated to the investigator.

6. If the reviewer determines that the event may be an unanticipated problem, the report is reviewed at a convened IRB meeting and follows notification procedures for UPs.

15 Unanticipated Problems Involving Risks to Participants or Others

Dartmouth complies with DHHS and FDA regulations which require organizations to have written policies on reporting unanticipated problems involving risks to subjects or others (UP) to the IRB, organizational officials and relevant federal agencies and departments. The following procedures describe how UPs are handled in research under the jurisdiction of Dartmouth. Unless specifically required by the IRB, the Dartmouth IRB does not accept reports of adverse events that do not meet the definition of a UP.

15.1 IRB Review

Upon submission of a UP report the report is reviewed by the IRB Office and IRB Chair or member designee. The reviewer has access to all study documents, including the complete study file, the current protocol, the currently approved consent/permission/assent document(s), previous UP reports and the investigator’s brochure (if applicable).

The reviewer makes findings, takes action or makes recommendations to the IRB based on the following considerations:

- Whether the reported event meets the definition of a UP;
- What action is appropriate in response to the report;
- Whether suspension or termination of approval is warranted.

1. If the reviewer determines that the event does not meet the definition of a UP or the UP involves no more than minimal risks to participants or others the reviewer may take any of the following actions:
   a. No action
   b. Requiring modifications to the protocol/research plan
   c. Revising the continuing review timetable
   d. Modifying the consent process
   e. Modifying the consent document
   f. Providing additional information to current participants (e.g., whenever the information may relate to participants’ willingness to continue participation)
g. Providing additional information to participants who have completed the study or withdrawn early

h. Requiring additional training of the investigator and/or study staff

i. Other actions as appropriate given the specific circumstances

2. If the reviewer finds that the event meets the definition of a UP and is more than minimal risk the reviewer refers the report to the next available meeting of the convened IRB and have it added to the meeting agenda. All IRB members have access to the report and supporting documentation and all study materials electronically.

The IRB may:

a. Require modifications to the protocol/research plan

b. Revise the review frequency for continuing review

c. Require a modification to the consent process

d. Require a modification to the consent/permission/assent document(s)

e. Require additional information be given to current participants, for example, when the event may relate to a participant’s willingness to continue participation

f. Require additional information be given to participants who have completed the study

g. Require additional training of the investigator and/or study staff

h. Reconsider approval

i. Require re-consent of participants currently enrolled

j. Require additional monitoring of the research

k. Require monitoring the consent process

l. Refer to other organizational entities (e.g., legal counsel, research compliance, risk management, Institutional Official) for additional review

m. Suspend approval

n. Terminate approval

o. Other actions as appropriate given the specific circumstances

2. If a report suggests imminent risk to participant safety, the IRB may immediately suspend or terminate the research.

3. If the IRB finds that the event is a UP and that suspension or termination of approval is warranted, the IRB notifies the investigator in writing of its findings, with copies to the Department Chair, the IO, and, relevant federal regulatory agencies, the sponsor and others as appropriate, following the requirements outlined in Section 8, Study Suspension and Termination.
16 Non-compliance

As part of its commitment to protecting the rights and welfare of human research participants, all Investigators and other study personnel involved in human research are required to comply with all laws and regulations governing their research activities, institutional policies and all requirements and determinations of the IRB.

The following procedures describe how complaints and allegations of non-compliance are handled by the IRB.

16.1 Definitions

**Non-compliance**: Non-compliance is defined as failure to adhere to federal, state, or local regulations or organizational policies related to human subject research, or the requirements or determinations of the IRB. Non-compliance may be minor, serious or continuing.

**Minor non-compliance**: Minor non-compliance is defined as non-compliance that, in the judgment of the IRB, does not increase risks to participants or others, does not compromise the scientific integrity of the study or affect the participant’s willingness to participate in the research.

**Serious non-compliance**: Serious non-compliance is defined as non-compliance that creates an increase in risks to participants, adversely affects the rights, welfare or safety of participants or others, may affect participants’ willingness to participate in the research or adversely affects the scientific integrity of the study. Willful violation of regulations and/or policies may also constitute serious non-compliance.

**Continuing non-compliance**: Continuing non-compliance is defined as a pattern of non-compliance that suggests a likelihood that instances of non-compliance will continue unless the IRB or organization intervenes.

**Allegation of Non-Compliance**: Allegation of Non-Compliance is defined as an unproven assertion of non-compliance.

**Finding of Non-Compliance**: Finding of Non-Compliance is defined as an allegation of non-compliance that is proven true or a report of non-compliance that is clearly true (for example, audit finding of an unsigned consent document, or admission by an investigator that the protocol/research plan was willfully not followed. A finding of non-compliance must be categorized as minor, serious or continuing.

16.2 Reporting

Investigators and their study staff are required to report instances of possible non-compliance to the IRB. The investigator is responsible for reporting possible non-compliance by study personnel. Any individual or employee may report observed or apparent instances of non-compliance. The reporting party is responsible for making the report in good faith, maintaining confidentiality and cooperating with any IRB and/or organizational review of the report.
If an individual, whether investigator, study staff or other, is uncertain whether there is cause to report non-compliance, he or she may contact the IRB Office Director, IRB Chair or the Office of Integrity and Compliance directly to discuss the situation informally.

Reports of alleged serious or continuing non-compliance must be submitted to the IRB Office within 10 working days of discovery. The report must include a complete description of the alleged non-compliance, including any personnel involved.

Reports of alleged minor non-compliance may be reported at the time of Continuing Review. If the IRB, or IRB Chair if review is by expedited review, finds the non-compliance to be serious or continuing, the review and reporting requirements for serious or continuing non-compliance are followed.

Reports may be made anonymously.

16.3 Review of Allegations of Non-compliance

All allegations of non-compliance are reviewed by the IRB Director and Chair or designee(s). The reviewer reviews the report or allegation and may request additional information or an audit of the research in question.

When a determination that non-compliance did not occur because the incident was within the limits of an approved protocol/research plan for the research involved, the determination is reported in writing to the investigator and, if applicable, the reporting party. The determination letter is copied to the Institutional Official and any other parties notified of the allegation at the outset.

If the report or allegation represents non-compliance, the non-compliance is processed according to Section 16.4 (Review of Findings of Non-compliance).

If an allegation or finding of non-compliance warrants suspension of the research before completion of any review or investigation to ensure protection of the rights and welfare of study participants, the IRB Chair may suspend the research as described in Section 8 with subsequent review by the IRB.

If additional expertise or assistance is required to complete the review or investigation and may request assistance from the IRB Office or form an ad hoc committee to assist with the review and fact gathering process. When an ad hoc committee assists in the review process, the Chair or designee is responsible for assuring that minutes of the meeting are generated and kept to help support any determinations or findings made by the ad hoc committee.

16.4 Review of Findings of Non-compliance

16.4.1 Minor Non-compliance:

When the Chair or designee determines that non-compliance occurred, but the non-compliance does not meet definition of serious or continuing non-compliance, the determination is reported in writing to the investigator and, if applicable, the reporting party. The Chair or designee reviews any corrective and preventive actions taken or proposed by the investigator
and determine if the actions are sufficient or if additional actions may be necessary. In the event that additional actions may be warranted, the matter is referred to the convened IRB for review.

16.4.2 Serious or Continuing Non-compliance

When the Chair or designee determines that non-compliance has occurred and that the non-compliance may meet the definition of serious or continuing non-compliance, the report of non-compliance is referred for review by the IRB at the next available convened meeting. The Chair or designee may call an emergency IRB meeting should the circumstances warrant.

The IRB may:

1. Find that there is no issue of non-compliance
2. Find non-compliance that is neither serious nor continuing and that an adequate corrective and/or preventive action plan is in place
3. Find serious or continuing non-compliance and require a corrective and/or preventive action plan or modification of a proposed plan
4. Find that additional information is required to make a final determination.

16.4.3 Final Review

Upon a finding of serious or continuing non-compliance, the IRB may take one or more of the following actions:

1. Request a corrective and/or preventive action plan from the investigator
2. Verify that participant selection is appropriate
3. Observation of the informed consent process
4. Require additional data and safety monitoring of the research activity
5. Request a directed audit of the study or specific areas of concern
6. Request a status report after each participant receives intervention
7. Modify the continuing review cycle/approval period
8. Require additional investigator and staff education
9. Require oversight by a senior investigator
10. Restrict, suspend or terminate the investigator’s research privileges
11. Require notification of the non-compliance to currently enrolled participants (for example, if the non-compliance might affect their willingness to continue participation)
12. Require modification(s) to the protocol/research plan and/or consent/permission/assent form(s).
13. Require notification of the non-compliance to participants whose participation has ended

14. Require re-consent of current participants

15. Suspend the study (See below)

16. Terminate the study (See below)

17. Other actions deemed appropriate by the IRB

Where the IRB determines that the non-compliance also meets the definition of an unanticipated problem involving risks to participants or others, it is also handled according to Section 15.

The investigator is informed of the IRB determination and the basis for the determination in writing. If the IRB determines that the non-compliance was serious or continuing, the results of the final review is reported as described in Section 18.

17 Complain
ts

The IRB Office Director, IRB Chair, or designee promptly handles (or delegates staff to handle), and, if necessary, investigate all complaints, concerns, and appeals received by the IRB Office. This includes complaints, concerns, and appeals from investigators, research participants and others.

Upon receipt of the complaint, the Director, Chair or designee makes a preliminary assessment whether the complaint warrants immediate suspension of the research project. If a suspension is warranted, the procedures in Section 8 are followed.

If the complaint may meet the definition of non-compliance, it is considered an allegation of non-compliance according to Section 16.

If the complaint may meet the definition of an unanticipated problem involving risk to participants or others, it is handled according to Section 15.

If the complaint is actually a query from a research participant regarding study procedures or payments not received it is forwarded to the investigator/study team for handling.

Promptly within receipt of the complaint, the Director or Chair formally acknowledges, either by letter or email, depending upon the original method of notification, that the complaint has been received and is being investigated, if the person making the complaint provided contact information.

18 Reporting to Regulatory Agencies and Organizational Officials

Federal regulations require prompt reporting to appropriate organizational officials and, as applicable, the federal department or agency head, of (i) any unanticipated problems involving risk to participants or others; (ii) any serious or continuing non-compliance with this policy or the requirements or determinations of the IRB; and (iii) any suspension or termination of IRB approval. Dartmouth IRB complies with this requirement as outlined below.
18.1 Procedures

When the IRB:

a. Determines that an event is considered an unanticipated problem involving risk to participants or others;

b. Determines serious or continuing non-compliance; or

c. Suspends or terminates approval of research

1) The IRB Office Director or designee prepares reports or letters that include the following information:

a. The nature of the event (Unanticipated problem involving risks to participants or others, serious or continuing non-compliance, suspension or termination of IRB approval of research);

b. Name of the institution conducting the research;

c. Title of the research project and/or grant proposal in which the problem occurred;

d. Name of the investigator on the project;

e. Number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement);

f. A detailed description of the problem including the findings of the organization and the reasons for the IRB’s decision;

g. Actions the institution is taking or plans to take to address the problem (e.g., revise the protocol/research plan, suspend enrollment, terminate the research, revise the informed consent document, inform participants, increase monitoring of participants, etc.);

h. Plans, if any, to send a follow-up or final report by a specific date, upon completion of an investigation or when a corrective action plan has been implemented;

2) The IRB Chair and the IO review the letter and recommend modifications as needed.

3) The IO or designee is the signatory for the report or letter.

4) A copy of the report is sent to:

a. The Institutional Official

b. The following federal agencies:

   • OHRP, if the study is subject to DHHS regulations or subject to a DHHS FWA.
• FDA, if the study is subject to FDA regulations.
• 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 federal agency, as required by the agency.
  o Reporting to a regulatory agency is not required if the event occurred at a site that was not subject to the direct oversight of the organization, and the agency has been notified of the event by the investigator, sponsor, another organization, or other mechanisms.

c. Investigator
d. Sponsor, if applicable
e. Investigator’s Department Chair
f. The Privacy Officer, if the event involved unauthorized use, loss, or disclosure of individually-identifiable patient information from a covered entity
g. The Information Security Officer, if the event involved violation of information security requirements
h. Office of Integrity and Compliance
i. Office of Sponsored Programs, if applicable
j. Office of Risk Management, if appropriate]
k. Others as deemed appropriate by the Institutional Official

The IRB Office Director ensures that all steps of this policy are completed promptly after the determination. For more serious actions, the Director expedites reporting.

19 Investigator Responsibilities

Investigators are responsible for the conduct of research. If tasks are delegated to appropriately trained and qualified members of the research team, investigators must maintain oversight for the conduct of those to whom they delegate responsibility and retain ultimate responsibility for the research.

19.1 Investigators

The research team is made up of ‘investigators’, differentiated as follows, along with their responsibilities in the conduct of research involving human participants.

Principal Investigators (PI)
The Dartmouth IRB recognizes one PI for each study. The PI has the ultimate responsibility for all research activities. At Dartmouth the PI is required to be a faculty or staff member, or an affiliate-faculty member.
The PI is responsible for ensuring that the research has sound research design and is appropriately supervised.

Studies that require expertise or skills beyond those held by the PI must either be modified or have expertise and skills supplemented by the inclusion of one or more additional qualified co-investigators.

19.2 Responsibilities

Investigators who conduct research involving human participants must:

1. Conduct research in accordance with the ethical principles in the Belmont Report;
2. Have a research plan that is scientifically sound and minimizes risk to participants;
3. Ensure that the study includes a plan for the just, fair, and equitable recruitment and selection of participants;
4. When some or all of the participants are likely to be vulnerable to coercion or undue influence (e.g., children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons), include additional safeguards in the study to protect the rights and welfare of these participants;
5. Ensure that the study includes adequate provisions for the monitoring of participants and data to ensure participant safety;
6. Ensure that there are adequate provisions to protect the privacy interests of participants;
7. Ensure that there are adequate provisions to protect data confidentiality and the interests of participants, including an information security plan that considers the collection, storage, maintenance, analysis, and transmission of data and other identifiable information, when applicable;
8. Have sufficient resources necessary to protect human participants, including:
   a. Access to a population that would allow recruitment of the required number of participant;
   b. Sufficient time to conduct and complete the research;
   c. Adequate number of qualified staff to conduct the research;
   d. Adequate facilities to conduct the research;
   e. Necessary equipment to conduct the research;
   f. A plan to ensure proper supervision of the research, including a plan for periods of absence or decreased availability;
   g. Availability of medical, psychological, or other support that participants might require during or as a consequence of participation in the research;
9. Assure that all procedures in a study are performed with the appropriate level of supervision and only by individuals who are licensed or otherwise qualified to perform such under the laws of New Hampshire and Dartmouth policies;

10. Assure that all study personnel are educated in the regulatory requirements regarding the conduct of research and the ethical principles upon which they are based;

11. Assure that all study personnel are adequately trained and informed about the research and their specific duties and functions.

12. Promptly report any changes in study personnel, including investigators, to the IRB for review and approval (investigators and staff may not begin work on the research until IRB-approved);

13. Protect the rights, safety, and welfare of research participants;

14. Ensure that legally effective HIPAA authorization is obtained for each research participant, if applicable, unless the IRB has approved a waiver of the requirement;

15. Ensure that the information in the consent/permission/assent form(s) is consistent with that in the protocol;

16. Obtain and document informed consent and ensure that no human research participant is involved in the research prior to obtaining consent or permission from the legally authorized representative, unless a waiver of the requirement has been approved by the IRB;

17. Have a procedure to receive questions, complaints, or requests for additional information from participants and respond appropriately;

18. Ensure that all information provided to the IRB is accurate and complete so that the IRB may fulfill its responsibilities to review the research and make the required determinations;

19. Ensure that all research involving human participants receives IRB review and approval or a determination of exemption in writing before research begins;

20. Ensure that all research involving human participants is reviewed by other organizational components and committees, as applicable;

21. Comply with all IRB decisions, conditions, and requirements;

22. Ensure that studies receive continuing IRB review and approval;

23. Report unanticipated problems, deviations, complaints, non-compliance, suspensions, terminations, and any other reportable events to the IRB;

24. Notify the IRB if information becomes available that suggests a change to the potential risks or benefits of the research;

25. Obtain IRB review and approval before changes are made to the research unless a change is necessary to eliminate apparent immediate hazards to participants;
26. Retain records for the time period and in the manner required by applicable regulations, contractual agreements and organizational policies.

Additional investigator responsibilities, including specific responsibilities for investigators engaged in FDA-regulated research are described elsewhere in this document.

19.3 Investigator Records

Investigators must comply with all sponsor record-keeping requirements, if applicable, and maintain the following research records:

19.3.1 Study Records

- Individual participant records
- Recruitment material
- Documentation of consent process (who, what, when and how)
- Signed consent forms
- Unanticipated Problem Reports
- Reports of Participant complaints
- Results of all procedures conducted on the participant, including final visit (if no final visit, reason why: e.g., removal from study, withdrawal from study, death)

19.3.2 Regulatory Records

- All IRB-approved versions of the protocol/research plan
- All correspondence to and from the IRB
- All correspondence with the sponsor and others regarding the study
- Continuing review progress reports
- Modification Requests
- Investigational product accountability records, when applicable

19.3.3 Record Retention

Dartmouth’s Record Retention policy, which includes provisions for ownership of data, must be followed. Study records must be retained in accordance with regulatory, organizational and sponsor or grantor requirements, but no less than six (6) years following completion of the research. All records must be maintained securely with limited access. Disposal of investigator records must be done in such a manner that no identifying information can be linked to research data.
19.4 Investigator Concerns

Investigators who have concerns regarding Dartmouth’s IRB or IRB(s) should convey them to the Institutional Official or other responsible party (e.g., supervisor, college dean, Department Chair), as appropriate, who may convey the concern to the IO. The IO considers the concern, and, if deemed necessary, seeks additional information. The IO may convene the parties involved, including the investigator, or a subcommittee to investigate and decide if procedural or policy modifications are warranted. In addition, the IRB Chair and/or the IRB Office Director are available to address investigators’ questions, concerns and suggestions.

In addition to these SOPs, which are made available on Dartmouth’s HRPP and IRB website, there is a link on the website for concerns (Ethics Point) or complaints.

20 Sponsored Research

It is Dartmouth policy that any sponsored research conducted under the jurisdiction of the Organization is conducted in accordance with federal guidelines and ethical standards as applicable. The following describe the procedures to ensure that all sponsored research meets this requirement.

20.1 Definitions

**Sponsor:** Sponsor means the company, institution, or organization responsible for the initiation, management or financing of a research study.

**Sponsored research:** Sponsored research means research funded through a grant or contract that involves a specified statement of work (e.g., the research proposal), including clinical trials involving investigational drugs, devices or biologics.

20.2 Responsibility

Sponsor grants, contracts, and other written agreements are reviewed for the following by the Office of Sponsored Programs or Clinical Trials Office, in consultation with the IRB Office, as necessary:

1. All contracts with a sponsor include a clause that addresses medical care for research participants with a research-related injury, when appropriate.
2. If the sponsor conducts research site monitoring visits or monitoring activities remotely, the contract includes a clause that the Sponsor promptly (no longer than 30 days) report findings that could affect the safety of participants or influence the conduct of the study to the investigator or Dartmouth.
3. If the sponsor has the responsibility to conduct data and safety monitoring, the contract includes a clause that addresses provisions for data monitoring to ensure the safety of participants and for providing data and safety monitoring reports to the investigator or Dartmouth.
4. In addition, in general, all contracts have language to the effect that all parties will abide by the applicable laws and regulations governing clinical research including 21CFR. 312.50 General responsibilities of sponsors: "...ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug." And

5. 21CFR.312.55 Informing investigators "(b) The sponsor shall, as the overall investigation proceeds, keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use."

6. Payment in exchange for referral of prospective participants from investigators (physicians) ("finder’s fees") is not permitted. Payment designed to accelerate recruitment that are tied to the rate or timing of enrollment ("bonus payments") is not permitted.

21 Conflict of Interest in Research

Openness and honesty are indicators of integrity and responsibility, characteristics that promote quality research and strengthen the research process. It is Dartmouth policy to preserve public trust in the integrity and quality of research by reducing actual or perceived conflict of interest ("COI") in the conduct of research. COI in research is any interest that competes with an organization’s or individual’s obligation to protect the rights and welfare of research participants, the integrity of a research study, or the credibility of the research program. A conflict of interest can be financial or non-financial. A conflict of interest should be eliminated when possible and disclosed and effectively managed when it cannot be eliminated.

21.1 Researcher Conflicts of Interest

The Dartmouth College Research Conflict of Interest Committee is based in the Provost Office and is managed by the Dartmouth Research Compliance Officer. Dartmouth’s IRB Office and IRBs collaborate with the COI Committees to ensure that COI of researchers and research staff (‘researchers’) are identified and managed before the IRB completes its review of any research application. The IRB Chairs and IRB Director (or designee) are members of the COI Committee. Determinations related to human subject research are made with input from the IRB perspective. Final determinations are the purview of the IRB.

21.1.1 Procedures

21.1.1.1 Disclosure of Researcher COI

For IRB purposes, researcher conflict review occurs at the time of new study submission, continuing review, and amendments to identify and add new study personnel or to disclose a new or changed interest. When a submission identifies the need for conflict review, the
researcher/study personnel with the conflict is responsible for reporting the potential conflict to the COI Officer. In the event a conflict that requires disclosure or management is identified, the COI Committee (with membership of the IRB) provide a summary of the financial relationship and the management plan (‘MP’) as approved by the COI Committee (with membership of the IRB).

**Evaluation of COI**

The COIC/IRB determine:

- Whether the COI affects the rights or welfare of research participants;
- Whether the COI might adversely affect the integrity or credibility of the research or the research program; and
- Whether the management plan (MP) effectively protects research participants and the integrity and credibility of the research and the research program.

**Considering:**

- How the research is supported or financed;
- The nature and extent of the financial relationship;
- The role and responsibilities of the individual in the design, conduct, and reporting of the research; and
- The ability of the individual to influence the outcome of the research.

### 21.1.1.2 Management of COI

The IRB has final authority to determine whether the research, the significant financial interest (SFI), and the MP, if any, allow the research to be approved. For studies where the COI Committee has approved a MP, the IRB shall either affirm the MP before approving the research or request changes to strengthen it.

The COIC / IRB may require:

1. Disclosure of the COI to research participants during the consent process and/or in the consent document;
2. Modification of the research plan or safety monitoring plan;
3. Monitoring of research by a third party;
4. Disqualification of the conflicted party from participation in all or a portion of the research;
5. Appointment of a non-conflicted PI;
6. Divestiture of significant financial interests;
7. Severance of relationships that create actual or potential conflicts.

In the event the conflict cannot be effectively managed, the IRB may disapprove the research.
21.2 IRB Member Conflict of Interest

No IRB member or alternate may participate in the review of any research in which the member has a conflict of interest (COI), except to provide information as requested. It is the responsibility of each IRB member to disclose any COI related to a study submitted for review and recuse him/herself from the deliberations and vote by leaving the room.

The IRB staff works to ensure that IRB members and alternates are not assigned to conduct reviews of studies for which the member has a conflict and ensures appropriate recusal during convened meetings.

IRB members, alternates, or consultants may be considered to have a conflicting interest requiring recusal when they, or an immediate member of their family, have any of the following:

1. Involvement in the design, conduct, and reporting of the research;
2. Significant financial interests related to the research being reviewed, as described in the Dartmouth Conflict of Interest Policy; or
3. Any other situation where an IRB member believes that another interest conflicts with his or her ability to deliberate objectively on a study.

The agenda at each IRB meeting reminds members that they must recuse themselves from the discussion and vote of a specific research study in which they have a conflict. If a conflicted member is participating by conference call, videoconference or web meeting, the member’s participation (connection) is terminated for discussion and voting.

IRB members with a conflicting interest are not counted towards quorum for the particular review and are not present for the vote. Recusals of members with COIs are recorded in the minutes.

21.3 Institutional Conflict of Interest

The Dartmouth College Conflict of Interest Policy requires disclosures to be made by certain individuals in senior leadership positions in connection with financial transactions, as follows:

The following persons shall also disclose in writing to the Office of General Counsel (OGC) on an annual basis on disclosure forms provided by that office information regarding certain financial transactions between Dartmouth College and such persons, or certain members of such persons’ families, or certain Entities in which such persons have an interest:

1. The trustees (including the President);
2. The Provost, the Vice, Assistant and Associate Provosts, the Vice Presidents, the Dean of Dartmouth College, the Deans of the Faculty of Arts and Sciences and the Professional Schools, and their respective principal financial officers;
3. Department chairs;
5. Administrators in the Purchasing Department, and senior administrators in the offices of the Deans and Vice Presidents; and

6. Such other employees as the General Counsel shall designate as being employees who, because of their respective duties and responsibilities, should disclose transactions with Dartmouth College to the OGC.

The above provisions are intended to help identify the existence of conflicts of interest that might arise from certain financial relationships of these individuals in light of the decision-making authority vested in them by the College.

The Office of Technology Transfer (TTO) and the Committee for the Protection of Human Subjects (CPHS) are represented on the Research Conflict of Interest Committee. The TTO maintains information related to intellectual property in which Dartmouth has an interest. In the past, the CPHS has utilized this information to make determinations regarding information which will be conveyed to potential research participants in the consent form.

Equity interests held by Dartmouth in early-stage companies (typically taken in accordance with the Dartmouth College Policy on Acceptance of Equity in connection with an IP licensing transaction) are held in trust by T. Rowe Price on Dartmouth’s behalf. Once placed in the trust, T. Rowe Price is vested with the authority, in its sole discretion, to make determinations as to when and whether to sell these securities, and Dartmouth will not be consulted on nor will it receive any prior notice of this decision to sell.

21.4 Recruitment Incentives

Payment arrangements among sponsors, organizations, investigators, and those referring research participants present a conflict of interest and may place participants at risk of coercion or undue influence or cause inequitable selection. Payment in exchange for referrals of prospective participants (“finder’s fees”) is not permitted. Similarly, payments designed to accelerate recruitment that are tied to the rate or timing of enrollment (“bonus payments”) are also not permitted.

22 Outreach

Dartmouth is committed to ensuring that educational opportunities are offered to research participants, prospective research participants, and members of the community, to enhance understanding of research involving human participants at Dartmouth and provide the opportunity for input and to express concerns.

22.1 Responsibility

The IRB Office Director and IO and stakeholders of the HRPP ensure the following as applicable:
22.2 Outreach Resources and Educational Materials

1. The HRPP websites includes information on how to contact Dartmouth with any questions or concerns about specific research projects or research in general and a listing of relevant research-related links.
2. Flyers and posters describing on-going are available at Dartmouth.
3. The HRPP websites includes a “Contact Us” link that allows members of the community to ask questions, express concerns, or provide feedback. Provision of contact information by the person is optional.
4. Dartmouth researchers periodically provide presentations related to research to community organizations.
5. Dartmouth Hitchcock Medical has ongoing displays (via posters) describing research throughout the facility.
6. Dartmouth Thayer School of Engineering and other graduate programs hold public forums describing current research projects.

22.3 Evaluation

The IRB Office Director or Associate Director, in consultation with the IO and/or IRB Chair(s), and HRPP stakeholders as appropriate, considers:

1. Community outreach activities in the past year;
2. Feedback provided via the “Contact Us” mechanism on the HRPP websites;
3. Feedback provided from other sources (unaffiliated IRB members, investigators, research staff, students, etc.).

The results of the review are used to evaluate the outreach activities and make changes as appropriate. The review is also used to identify additional resources that may be needed to meet the outreach needs of the research community.

23 Health Insurance Portability and Accountability Act (HIPAA)

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) required the creation of a Privacy Rule for identifiable health information. While the primary impact of the Privacy Rule is on the routine provision of and billing for health care, the Rule also affects the conduct and oversight of research.

The Privacy Rule defines individually identifiable health information transmitted or maintained by a covered entity in any form (electronic, written or oral) as “protected health information” (PHI) and establishes the conditions under which investigators may access and use this information in the conduct of research.
Under the Privacy Rule, a HIPAA Authorization may be combined with the consent document for research. When the consent document is combined with an Authorization as it is at Dartmouth, 45 CFR part 46 and 21 CFR part 56 require IRB review of the combined document.

23.1 Definitions (from the NIH HIPAA Privacy Booklet for Research)

Access: Access is the mechanism of obtaining or using information electronically, on paper, or other medium for the purpose of performing an official function.

Accounting of Disclosures: Information that describes a covered entity’s disclosures of PHI other than for treatment, payment, and health care operations; disclosures made with Authorization; and certain other limited disclosures. For those categories of disclosures that need to be in the accounting, the accounting must include disclosures that have occurred during the 6 years (or a shorter time period at the request of the individual) prior to the date of the request for an accounting. However, PHI disclosures made before the compliance date for a covered entity are not part of the accounting requirement.

Authorization: An individual’s written permission to allow a covered entity to use or disclose specified PHI for a particular purpose. Except as otherwise permitted by the Privacy Rule, a covered entity may not use or disclose PHI for research purposes without a valid Authorization.

Covered entity: A health plan, a health care clearinghouse, or a health care provider who transmits health information in electronic form in connection with a transaction for which DHHS has adopted a standard.

Data Use Agreement: An agreement into which the covered entity enters with the intended recipient of a limited data set that establishes the ways in which the information in the limited data set may be used and how it is protected.

Designated Record Set: A group of records maintained by or for a covered entity that includes (1) medical and billing records about individuals maintained by or for a covered health care provider; (2) enrollment, payment, claims adjudication, and case or medical management record systems maintained by or for a health plan; or (3) used, in whole or in part, by or for the covered entity to make decisions about individuals. A record is any item, collection, or grouping of information that includes PHI and is maintained, collected, used, or disseminated by or for a covered entity.

Disclosure: The release, transfer, access to, or divulging of information in any other manner outside the entity holding the information.

Health Information: Health Information means any information, whether oral or recorded in any form or medium, that (1) is created or received by a health care provider, health plan, public health authority, employer, life insurer, school or university, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or
condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual.

**Individually Identifiable Health Information:** Information that is a subset of health information, including demographic information collected from an individual, and (1) is created or received by a health care provider, health plan, employer, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; and (a) that identifies the individual; or (b) with respect to which there is a reasonable basis to believe the information can be used to identify the individual.

**Limited Data Set:** PHI that excludes 16 categories of direct identifiers and may be used or disclosed, for purposes of research, public health, or health care operations, without obtaining either an individual’s Authorization or a waiver or alteration of Authorization with a data use agreement.

**Minimum Necessary:** The standard that uses the least information reasonably necessary to accomplish the intended purpose of the use, disclosure, or request. Unless an exception applies, this standard applies to a covered entity when using or disclosing PHI or when requesting PHI from another covered entity. A covered entity that is using or disclosing PHI for research without Authorization must make reasonable efforts to limit PHI to the minimum necessary. A covered entity may rely, if reasonable under the circumstances, on documentation of IRB or Privacy Board approval or other appropriate representations and documentation under section 164.512(i) as establishing that the request for protected health information for the research meets the minimum necessary requirements.

**Privacy Board:** A board that is established to review and approve requests for waiver or alteration of Authorization in connection with the use or disclosure of PHI as an alternative to obtaining waiver or alteration from an IRB. A Privacy Board consists of members with varying backgrounds and appropriate professional competencies as necessary to review the effect of the research plan on an individual’s privacy rights and related interests. The board must include at least one member who is not affiliated with the covered entity, is not affiliated with any entity conducting or sponsoring the research, and is not related to any person who is affiliated with any such entities. A Privacy Board cannot have any member participating in a review of any project in which the member has a conflict of interest.

**Protected Health Information:** PHI is individually identifiable health information transmitted by electronic media, maintained in electronic media, or transmitted or maintained in any other form or medium. PHI excludes individually identifiable health information in education records covered by the Family Educational Rights and Privacy Act, as amended, 20 U.S.C. 1232g, records described at 20 U.S.C. 1232g(a)(4)(B)(iv), and employment records held by a covered entity in its role as employer.
**Research:** A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. This includes the development of research repositories and databases for research.

**Use:** The sharing, employment, application, utilization, examination, or analysis of individually identifiable health information within the entity or health care component (for hybrid entities) that maintains such information.

**Waiver or Alteration of Authorization:** The documentation that the covered entity obtains from an investigator, IRB or Privacy Board that grants a waiver or alteration of the Privacy Rule’s requirement that an individual must authorize a covered entity to use or disclose the individual’s PHI for research purposes.

**Workforce:** Employees, volunteers, trainees, and other persons whose conduct, in the performance of work for a covered entity, is under the direct control of the covered entity, whether or not they are paid by the covered entity.

**23.2 The IRB’s Role under the Privacy Rule**

Under the Privacy Rule, IRBs were given the authority to consider, and act upon, requests for a partial or complete waiver or alteration of the Privacy Rule's Authorization requirement for uses and disclosures of PHI for research. Although DHHS and FDA Protection of Human Subjects Regulations include protections to help ensure the privacy of research participants and the confidentiality of information, the Privacy Rule supplements these protections by requiring covered entities to implement specific measures to safeguard the privacy of PHI. If certain conditions are met, an IRB may grant a waiver or an alteration of the Authorization requirement for research uses or disclosures of PHI.

Currently, the Dartmouth IRBs fulfill the functions of a Privacy Board for human research.

When acting upon a request to waive or alter the Authorization requirement, the IRB must follow the procedural requirements of the DHHS Protection of Human Subjects regulations and, if applicable, FDA regulations, including the review procedure (convened or expedited).

The researcher provides information on the CPHS required Forms to document required information. In addition, the IRB documents in the letter of approval of a waiver or alteration of the authorization requirement, both items (CPHS Form and IRB approval letter) includes:

- The identity of the approving IRB (if Full Committee review required)
- The date on which the waiver or alteration was approved
- Within the CPHS Form: A brief description of the PHI for which use or access has been determined by the IRB to be necessary in connection with the specific research activity

Dartmouth will not release PHI to investigators without individual authorization or proper documentation of IRB approval of a waiver or alteration of the requirement.
23.3 Authorization

Except as otherwise permitted, the Privacy Rule requires that a research participant authorize the use or disclosure of his/her PHI in research. This authorization is distinct from the participant’s consent to participate in research, which is required under the Common Rule and FDA regulations. A valid authorization must contain required statements and core elements [45 CFR 164.508(c)]. At Dartmouth authorization language is incorporated into the research consent document. Template consent documents, which include the required HIPAA authorization elements, are available on the HRPP and IRB Office websites.

Once executed, a signed copy is provided to the individual providing authorization. Signed authorizations are retained by Dartmouth for at least 6 years from the date of creation or the date it was last in effect, whichever is later.

A research participant has the right to revoke his/her authorization at any time. Investigators are not required to retrieve information that was disclosed under the authorization before learning of the revocation. Additionally, investigators may continue to use and disclosure PHI already obtained for the research under an authorization to the extent necessary to protect the integrity of the research.

When an authorization is obtained for research purposes, the Privacy Rule requires that it pertain only to a specific research study, not to nonspecific research or to future, unspecified projects. The Privacy Rule considers the creation and maintenance of a research repository or database as one specific research activity. The subsequent use or disclosure by a covered entity of information from the database for a specific research study requires separate authorization, unless a waiver of the requirement is granted.

When an Authorization permits disclosure of PHI to a person or organization that is not a covered entity (such as a sponsor or funding source), the Privacy Rule does not continue to protect the PHI disclosed to such entity. However, other federal and state laws and agreements between the covered entity and recipient, such as a Business Associate Agreement (BAA) or Confidentiality Agreement, may establish continuing protections for the disclosed information. Under the DHHS and FDA Human Subjects regulations, an IRB may impose further restrictions on the use or disclosure of research information to protect subjects.

Authorization Core Elements (depicted in the CPHS consent form templates):

1. A description of the PHI to be used or disclosed, identifying the information in a specific and meaningful manner.
2. The names or other specific identification of the person or persons (or class of persons) authorized to make the requested use or disclosure.
3. The names or other specific identification of the person or persons (or class of persons) to whom the covered entity may make the requested use or disclosure.
4. A description of each purpose of the requested use or disclosure.
5. Authorization expiration date or expiration event that relates to the individual or to the purpose of the use or disclosure (“end of the research study” or “none” are permissible for research, including for the creation and maintenance of a research database or repository).

6. Signature of the individual and date. If the individual’s legally authorized representative signs the Authorization, a description of the representative’s authority to act for the individual must also be provided.

Authorization Required Statements:

1. A statement of the individual’s right to revoke his/her Authorization and how to do so, and, if applicable, the exceptions to the right to revoke his/her Authorization or reference to the corresponding section of the covered entity’s notice of privacy practices.

2. Whether treatment, payment, enrollment, or eligibility of benefits can be conditioned on Authorization, including research-related treatment and consequences of refusing to sign the Authorization, if applicable.

3. A statement of the potential risk that PHI will be re-disclosed by the recipient. This may be a general statement that the Privacy Rule may no longer protect health information disclosed to the recipient.

23.4 Waiver or Alteration of the Authorization Requirement

The Privacy Rule contains criteria for waiver or alteration of authorization. If a covered entity has used or disclosed PHI for research pursuant to a waiver or alteration of authorization, documentation of the approval of the waiver or authorization must be retained for 6 years from the date of its creation or the date it was last in effect, whichever is later.

For research uses and disclosures of PHI, the IRB may approve a waiver or alteration of the authorization requirement in whole or in part. A complete waiver of authorization occurs when the IRB determines that no authorization is required for a covered entity to use and disclose PHI for a particular research project. A partial waiver of authorization occurs when the IRB determines that a covered entity does not need authorization for all PHI uses and disclosures for research purposes, such as accessing PHI for research recruitment purposes. The IRB may also approve a request that removes some PHI, but not all, or alters the requirements for an authorization.

In order for the IRB to waive or alter authorization, the Privacy Rule (45 CFR 164.512(i)(2)(ii)) requires the IRB to determine the following:

1. The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:
a. An adequate plan to protect health information identifiers from improper use and disclosure.

b. An adequate plan to destroy identifiers at the earliest opportunity consistent with conduct of the research (absent a healthcare or research justification for retaining them or a legal requirement to do so).

c. Adequate written assurances that the PHI will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

2. The research could not practicably be conducted without the waiver or alteration.

3. The research could not practicably be conducted without access to and use of the PHI.

The Privacy Rule allows institutions to rely on a waiver or an alteration of Authorization obtained from a single Privacy Board to be used to obtain or release PHI in connection with a multi-site project. However, DHHS also recognizes that “covered entities may elect to require duplicate Privacy Board reviews before disclosing [PHI] to requesting researchers” (67 Federal Register 53232, August 14, 2002). At Dartmouth, PHI may be disclosed for the purposes of research pursuant to a waiver provided by a non-Dartmouth Privacy Board if all required statements of conditions for the waiver are present. For PHI obtained at Dartmouth-Hitchcock, the privacy manager provides additional review for requested data.

23.5 Activities Preparatory to Research

Under the preparatory to research provision of the Privacy Rule, a covered entity may permit an investigator who works for that covered entity to use PHI for purposes preparatory to research such as assessing the feasibility of conducting a research project, developing a grant application, or identifying potential participants. A covered entity may also permit, as a disclosure of PHI, a researcher who is not a workforce member of that covered entity to review PHI (within that covered entity) for purposes preparatory to research.

The covered entity must obtain from the investigator representations that (1) the use or disclosure is requested solely to review PHI as necessary to prepare a research plan or for similar purposes preparatory to research, (2) the PHI will not be removed from the covered entity in the course of review, and (3) the PHI for which use or access is requested is necessary for the research.

At Dartmouth, these representations are generally made by the investigator submitting a Preparatory to Research request to the Privacy Manager at Dartmouth-Hitchcock Medical Center.
23.6 Research Using Decedent's Information

At Dartmouth, these representations are made by the investigator submitting a request to the Privacy Manager at Dartmouth-Hitchcock Medical Center.

(A) Representation that the use or disclosure sought is solely for research on the protected health information of decedents; (B) Documentation, at the request of the covered entity, of the death of such individuals; and (C) Representation that the protected health information for which use or disclosure is sought is necessary for the research purposes.

23.7 Future Uses: Databases and Repositories

The Privacy Rule recognizes the creation of a research database or a specimen repository to be a research activity if the data/specimens to be stored contain PHI. There are two separate activities that the covered entity must consider: (1) the use or disclosure of PHI for creating a research database or repository; and (2) the subsequent use or disclosure of PHI in the database for a particular research plan.

Individual authorization for the storage of PHI for future research must be sought unless the IRB has determined that the criteria for a waiver of the authorization requirement are satisfied. See Section 23.4 for a discussion of waiver of authorization.

The combined consent/authorization for future research must describe the future research uses in sufficient detail to allow the potential participant to make an informed decision. The investigator and IRB should be cognizant of uses of information/specimens that the target community may consider particularly sensitive, such as genetics, mental health, studies of origin, and use of tissues that may have cultural significance.

The consent/authorization for future research may be a stand-alone document or may be incorporated into another consent/authorization if the information/specimens originate from another research activity, such as a clinical trial, unless the research involves the use or disclosure of psychotherapy notes. Authorizations for the use or disclosure of psychotherapy notes can only be combined with another authorization for a use or disclosure of psychotherapy notes.

23.8 Ancillary Studies

Participation in ancillary studies not essential to the primary aims of the research should be on a voluntary basis. This is particularly important when the primary research offers a potential benefit, such as treatment, that might compel the potential participant to agree to something that he/she otherwise would not.

HIPAA reinforces this ethical principle by explicitly stating that authorization for “unconditioned” activities, for which there is no associated treatment, benefit or other effect on the individual participant cannot be required. Authorization for unconditioned activities must involve a clear opt-in mechanism.
It is acceptable to combine the authorization for a conditioned activity, such as a clinical trial, with authorization for an unconditioned activity, such as a corollary or sub-study that does not directly benefit or effect the individual participant, provided that:

1. The authorization clearly differentiates between the conditioned and unconditioned research activities;
2. The authorization clearly allows the individual the option to opt in to the unconditioned research activities; and
3. Sufficient information is provided for the individual to be able to make an informed choice about both the conditioned and unconditioned activities.

Separate authorization must be obtained for each research activity that involves the use and disclosure of psychotherapy notes. For example, authorization for the use and disclosure of psychotherapy notes for a clinical trial cannot be combined with an authorization for the use and disclosure of those psychotherapy notes for a corollary research activity.

23.9 De-identification of PHI under the Privacy Rule

Covered entities may use or disclose health information that is de-identified without restriction under the Privacy Rule. The “Safe Harbor” method permits a covered entity to de-identify data by removing all 18 data elements that could be used to identify the individual or the individual’s relatives, employers, or household members. Under this method, the identifiers that must be removed are the following:

1) Names;
2) All geographic subdivisions smaller than a state, including street address, city, county, precinct, ZIP Code, and their equivalent geographical codes, except for the initial three digits of a ZIP Code if, according to the current publicly available data from the Bureau of the Census:
   a. The geographic unit formed by combining all ZIP Codes with the same three initial digits contains more than 20,000 people.
   b. The initial three digits of a ZIP Code for all such geographic units containing 20,000 or fewer people are changed to 000.
3) All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older.
4) Telephone numbers;
5) Facsimile numbers;
6) Electronic mail addresses;
7) Social security numbers;
8) Medical record numbers;
9) Health plan beneficiary numbers;
10) Account numbers;
11) Certificate/license numbers;
12) Vehicle identifiers and serial numbers, including license plate numbers;
13) Device identifiers and serial numbers;
14) Web universal resource locators (URLs);
15) Internet Protocol (IP) address numbers;
16) Biometric identifiers, including fingerprints and voiceprints;
17) Full-face photographic images and any comparable images;
18) Any other unique identifying number, characteristic, or code, unless otherwise permitted by the Privacy Rule for re-identification.

Alternatively, a qualified statistician may certify that the risk is very small that health information could be used, alone or in combination with other available information, to identify individuals. The qualified statistician must document the methods and results of the analysis that justify such a determination. This analysis must be retained by the covered entity for 6 years from the date of its creation or when it was last acted on, whichever is later.

The Privacy Rule permits a covered entity to assign to, and retain with, the de-identified health information, a code or other means of record re-identification if that code is not derived from or related to the information about the individual and is not otherwise capable of being translated to identify the individual. The covered entity may not use or disclose the code or other means of record identification for any other purpose and may not disclose its method of re-identifying the information.

23.10 Limited Data Sets and Data Use Agreements

Limited data sets are data sets stripped of certain direct identifiers. Limited data sets may be used or disclosed only for public health, research, or health care operations purposes. The following direct identifiers must be removed for PHI to qualify as a limited data set:

1) Names;
2) Postal address information, other than town or city, state, and ZIP code;
3) Telephone numbers;
4) Fax numbers;
5) Email addresses;
6) Social security numbers;
7) Medical record numbers;
8) Health plan beneficiary numbers;
9) Account numbers;
10) Certificate or license numbers;
11) Vehicle identifiers and license plate numbers;
12) Device identifiers and serial numbers;
13) URLs;
14) IP addresses;
15) Biometric identifiers; and
16) Full-face photographs and any comparable images.

Before disclosing a limited data set, a covered entity must enter into a data use agreement (DUA) with the recipient. The data use agreement establishes the parameters around the proposed uses and disclosures of the data, who is permitted to have access to the data, and stipulates that no other use will be made of the data, no attempt will be made to identify or contact individuals whose data are included in the limited data set, that appropriate safeguards are in place to protect the data from unauthorized use and that the recipient will report any uses or disclosures of the PHI that they become aware of that are not in keeping with the terms of the DUA. Data Use Agreements for the purposes of research are available through the Dartmouth Office of Sponsored Projects and Dartmouth-Hitchcock Office of General Counsel and the Clinical Trials Office (CTO).

23.11 Research Participant Access to PHI

With few exceptions, the Privacy Rule guarantees individuals access to their medical records and other types of health information. One exception is during a clinical trial, when the participant’s right of access may be suspended while the research is in progress. The participant must be notified of and agree to the temporary denial of access when providing consent and authorization. Any such notice must also inform the individual that the right to access will be restored upon conclusion of the clinical trial. Language accommodating this exclusion is included in the applicable Dartmouth research consent/authorization templates.

23.12 Accounting of Disclosures

The Privacy Rule grants individuals the right to a written “Accounting of Disclosures” of their Protected Health Information made by a covered entity without the individual’s authorization in the six years prior to their request for an Accounting. A covered entity must therefore keep records of such PHI disclosures for 6 years.
Disclosure of PHI means communicating that information to a person or entity outside the covered entity. The Privacy Rule restricts both uses and disclosures of PHI, but it requires an accounting only for certain PHI disclosures.

An Accounting of Disclosures is required for:

1) Routinely Permitted Disclosures (e.g., under public health authority, to regulatory agencies, to persons with FDA-related responsibilities) with limited exceptions (e.g., law enforcement, national security, etc.);

2) Disclosures made pursuant to:
   a. Waiver of Authorization;
   b. Research on Decedents’ Information;
   c. Reviews Preparatory to Research.

An accounting is not needed when the PHI disclosure is made:

1) For treatment, payment, or health care operations;
2) Under an Authorization for the disclosure;
3) To an individual about himself or herself;
4) As part of a limited data set under a data use agreement.

The Privacy Rule allows three methods for accounting for research-related disclosures that are made without the individual’s Authorization or other than a limited data set: (1) A standard approach, (2) a multiple-disclosures approach, and (3) an alternative for disclosures involving 50 or more individuals. Whatever approach is selected, the accounting is made in writing and provided to the requesting individual. Accounting reports to individuals may include results from more than one accounting method.

24 Information Security

Dartmouth has established standards and safeguards to protect patient information and to ensure compliance with federal and state information security regulations. It is the responsibility of investigators to familiarize themselves with and comply with these standards. The use of personal laptops, desktops, portable/USB drives, and other non-Dartmouth devices for storage of research data is discouraged. Additionally, any potential or known breach of a device or of research data must be immediately reported to the IRB and Privacy Officer (as applicable).

Provisions for Data Security must be described in applications to the IRB and updated as necessary. When information containing direct identifiers such as Social Security numbers or PHI including data considered sensitive is to be transferred outside of the institution, the provisions for data security may be subject to further review and approval by the Dartmouth Research Privacy Officer or Dartmouth – Hitchcock Privacy Officer.
25 Special Topics

25.1 Community Based Research

Community based research (CBR) is research that is conducted as an equal partnership between academic investigators and members of a community. In CBR projects, the community participates fully in all aspects of the research process. Community is often self-defined, but general categories of community include geographic community, a community of individuals with a common problem or issue, or a community of individuals with a common interest or goal.

Where research is being conducted in communities, investigators are encouraged to involve members of the community in the research process, including the design and implementation of research and the dissemination of results when appropriate. The Dartmouth IRB Office assists investigators in developing such arrangements.

The most significant community involvement is in a subset of CBR called Community Based Participatory Research (CBPR) where there is an equal partnership between academic investigators and members of a community, with the community members actively participating in all phases of the research process, including the design and implementation of research and the dissemination of results when appropriate.

Questions to be considered as CBR studies are developed, and issues that the IRB considers when reviewing CBR include, but are not limited to:

- How is the community involved or consulted in defining the need for the proposed research (i.e., getting the community’s agreement to conduct the research)?
- How is the community involved or consulted in generating the study research plan?
- How are research procedures, including recruitment strategies and consent processes assessed to ensure sensitivity and appropriateness to various communities (e.g., literacy issues, language barriers, cultural sensitivities, etc.)?
- How is the community involved in the conduct of the proposed research?
- How are community members who participate in the implementation of the research trained and supervised?
- How have “power” relationships between investigators and community members on the research team, and in recruitment strategies been considered to minimize coercion and undue influence?
- What are the risks and benefits of the research for the community as a whole?
- How are boundaries between multiple roles (e.g., investigator, counselor, peer) be maintained, i.e., what happens when the investigator/research staff is the friend, peer, service provider, doctor, nurse, social worker, educator, funder, etc.)?
• How are research outcomes disseminated to the community?

• Is there a partnership agreement, letter, or memorandum of understanding signed by Dartmouth or the Dartmouth investigator and the community partner(s) that describes how they work together? If so, it should be uploaded with the application.

When CBR studies are proposed, the above information will be included in the submission materials. Dartmouth subscribes to the CITI (Collaborative Institutional Training Initiative) including the Community Based Research modules as an educational resource.

25.2 International Research

The Dartmouth IRB reviews all international human research over which it has jurisdiction to assure adequate provisions are in place to protect the rights and welfare of research participants. All policies and procedures that are applied to research conducted domestically are applied to international research, as appropriate. Approval of research is permitted if “the procedures prescribed by the foreign institution afford protections that are at least equivalent to those provided in [45 CFR 46 101 (h)].”

The Dartmouth IRB seeks sufficient knowledge of the local research context by requesting approval for the project from local IRBs or ethics committees (which may or may not be OHRP-registered) and/or local letters of support. The source of this information depends on the nature of the study, the country and the resources available to the investigator. Where there is a local IRB/IEC, Dartmouth’s IRB must receive and review the foreign institution or site’s IRB/IEC review and approval of each study prior to beginning the research at the foreign institution or site.

In settings where there are no IRBs/IECs, Dartmouth’s IRB may require additional verification and information from people outside the particular research project who are familiar with the customs, practices, or standards of care where the research takes place, including other applicable committees, other Dartmouth investigators with knowledge of the region, or a consultant who is an expert on the region, prior to approval. These individuals may either provide a written review of a particular research plan or attend an IRB meeting to provide the IRB with recommendations based on his or her expertise.

For Federally funded research, approval of research for foreign institutions or sites “engaged” in research is only permitted if the foreign institution or site holds an Assurance with OHRP and local IRB review and approval is obtained.

In most cases, approval of research for foreign institutions or sites “not engaged” in research is permitted if one or more of the following circumstances exist:

• When the foreign institution or site has an established IRB/IEC, the investigator must obtain approval to conduct the research at the "not engaged" site from the site’s IRB/IEC or provide documentation that the site’s IRB/IEC has determined that approval is not necessary for the investigator to conduct the proposed research at the site.
• When the foreign institution or site does not have an established IRB/IEC, a letter of cooperation must be obtained demonstrating that the appropriate institutional or oversight officials permit the research to be conducted at the performance site.
• IRB approval to conduct research at the foreign institution or site is contingent upon receiving documentation of the performance site’s IRB/IEC determination, or letter of cooperation, as applicable.

25.2.1.1 IRB Responsibilities

In addition to normal IRB review practices and applicable policies, the IRB considers the following during its review:

1. Qualifications of the investigator and research staff to conduct research in that country, including knowledge of relevant laws, regulations, guidance and customs.
2. Whether the consent process and consent documents are appropriate for the language(s) of participants and communication with the participant population and that arrangements are made to be able to communicate with participants throughout the study.
3. How modifications to the research are handled.
4. How complaints, non-compliance, protocol/research plan deviations and unanticipated problems involving risks to participants or others are handled.
5. How post-approval monitoring is conducted.
6. Whether the investigator has obtained the appropriate host country permissions to conduct research (e.g., institutional, governmental or ministerial, IRB, local or tribal). When appropriate, the IRB communicates and coordinates with the local institutions or ethics committees.
7. Mechanisms for communicating with the investigator and research staff when they are conducting the research in other countries.

25.2.1.2 Investigator Responsibilities

1. Assure that the resources and facilities are appropriate for the nature of the research.
2. Confirm the qualifications of the investigators and research staff for conducting research in that country(ies).
3. Obtain all appropriate host country permissions to conduct research (e.g., institutional, governmental or ministerial, IRB, local or tribal).
4. Ensure that the consent process and consent document are appropriate for the language(s) of participants and communication with the participant population and arrangements are made to be able to communicate with participants throughout the study.
5. Ensure that the following activities occur:
   a. Initial review, continuing review and amendments
   b. Post-approval monitoring
c. Handling of complaints, non-compliance and unanticipated problems involving risk to participants or others.

6. The Investigator does not rely upon an IRB or IEC that does not have policies and procedures for the activities listed above.

7. The Investigator considers how complaints, non-compliance, protocol/research plan deviations and unanticipated problems involving risks to participants or other are communicated to the IRB.

8. Notify the IRB promptly if a change in research activities alters the performance site’s engagement in the research (e.g., performance site “not engaged” begins to obtain consent of research participants, etc.).

9. Cooperate with the IRB regarding how and when post-approval monitoring is conducted.

10. The Investigator has mechanisms in place for communicating with the IRB.

25.2.1.3 Consent Documents

When applicable written informed consent documents must be in a language understandable to the proposed participant. When possible, the IRB reviews the document and a back translation of the exact content contained in the foreign language informed consent document.

25.2.1.4 Monitoring of Approved International Research

The IRB is responsible for the ongoing review of international research conducted under its jurisdiction through the continuing review process in accordance with all applicable federal regulations. When the IRB and a local ethics committee are both involved in the review of research, there is a plan for coordination and communication with the local IRB/IECs.

The IRB may request documentation of relevant correspondence between the Dartmouth investigator and the foreign institution or site and may require verification from sources other than the Dartmouth investigator that there have been no substantial changes in the research since its last review.

25.3 Research Repositories and Research Involving Coded Private Information or Biological Specimens

25.3.1 Biological Specimens

All activities involving the collection of human biological specimens that meet the definition of human subjects research, as well as the research use of specimens collected for clinical care, must be conducted under the terms of an IRB approved research protocol. The collection and use of human biological specimens (either identifiable or de-identified) must comply with all applicable laws and regulations for research involving human biological specimens or any superseding requirements. See CPHS Data Specimens Form.
25.3.2 Regulatory Oversight

Under HSS regulations, a human subject is a living individual about whom an investigator conducting research obtains

- data through intervention or interaction with the individual, or
- identifiable private information

Whether research involving biological specimens meets the definition of human subjects research is based on a) how the specimens were obtained and b) whether the specimens include identifiable private information.

If the specimens are obtained specifically for research purposes, then they have been collected through intervention or interaction with the individual and the research meets the definition of human subjects research. If the specimens were not collected for research purposes but as part of routine clinical care or other non-research purpose, then the research only meets the definition of human subjects research if the specimens include identifiable private information (See below for policies on coded specimens).

FDA regulations do not apply to biological specimens unless they are gathered as part of a clinical investigation involving human subjects or being used to test a medical device (See Section 13 for more detail on FDA regulations). HIPAA does not cover biological specimens but does cover protected health information (PHI) linked to the specimens (See Section 23 for more detail on HIPAA).

If the research meets the definition of human subjects research, then all of the requirements of this document apply. The CPHS has a “Not human subjects research” form to assist with these determinations.

25.3.3 IRB Review

Research involving only biological specimens may be exempt under Exemption Category #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.” However, for federally funded research, in order to qualify under this category, all of the specimens must exist prior to the research being submitted to the IRB.

Federally funded non-exempt research only involving biological specimens may be eligible for expedited review if it is minimal risk and falls within one of the following categories:

- Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture [with restrictions]
- Prospective collection of biological specimens for research purposes by noninvasive means
• Research involving materials... that have been collected, or will be collected solely for
nonresearch purposes or for previous research (per OHRP guidance).

All federally funded non-exempt research involving biological specimens that is not eligible for
expedited review must be reviewed at a convened IRB meeting.

Informed consent and documentation of consent is required for all non-exempt research
involving biological specimens, unless the requirement is waived by the IRB.

25.3.4 Coded Human Data or Biological Specimens

Dartmouth IRB policy is based on the OHRP guidance document entitled, “Guidance on
Research Involving Coded Private Information or Biological Specimens” (October 16, 2008
http://www.hhs.gov/ohrp/policy/cdebiol.html). This document:

1. Provides guidance as to when research involving coded private information or
specimens is or is not research involving human subjects, as defined under HHS
regulations for the protection of human research subjects (45 CFR Part 46).

2. Reaffirms OHRP policy that, under certain limited conditions, research involving only
coded private information or specimens is not human subjects research.

3. Clarifies the distinction between (a) research involving coded private information or
specimens that does not involve human subjects and (b) human subjects research that is
exempt from the requirements of the HHS regulations.

4. References pertinent requirements of the HIPAA Privacy Rule that may be applicable to
research involving coded private information or specimens.

Note: The FDA definition of human subjects differs from the Common Rule definition. Use of
coded specimens for FDA-regulated research such as research on In Vitro Diagnostic Devices
requires assessment according to the FDA regulations and guidelines. Investigators should
contact the IRB Office for guidance.

For purposes of this policy, coded means that: (1) identifying information (such as name or
social security number) that would enable the investigator to readily ascertain the identity of
the individual to whom the private information or specimens pertain has been replaced with a
number, letter, symbol, or combination thereof (i.e., the code); and (2) a key to decipher the
code exists, enabling linkage of the identifying information to the private information or
specimens.

Guidance:

Obtaining identifiable private information or identifiable specimens for research purposes
constitutes human subjects research. Obtaining identifiable private information or identifiable
specimens includes, but is not limited to:
1. Using, studying, or analyzing identifiable private information or identifiable specimens that have been provided to the investigator from any source for research purposes; and

2. Using, studying, or analyzing identifiable private information or identifiable specimens that were already in the possession of the investigator for research purposes.

Private information or specimens are considered to be individually identifiable when they can be linked to specific individuals by the investigator(s) either directly or indirectly with a code.

Research involving only coded private information or specimens do not involve human subjects per the Common Rule definition if both of the following conditions are met:

1. The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and

2. The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because:
   1. The investigators and the holder of the key enter (e.g. pathology lab) into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased (note that the HHS regulations do not require the IRB to review and approve this agreement);
   2. There are operating procedures for a repository or data management center that prohibit the release of the key to the investigators.

25.3.5 Who Should Determine Whether Coded Private Information or Specimens Is Human Subjects Research

The investigator, in consultation with the IRB Office, determines if the research involving coded information or specimens requires IRB review. If the request is verbal (by phone or in person) or by email, it is the investigator’s responsibility to maintain documentation of such request and decision. If the investigator submits a formal submission, the request must include sufficient documentation of the activity to support the determination. Formal submissions are responded to in writing and a copy of the submitted materials and determination letter kept on file as applicable. The “Not human subject research” Form assists with this determination.

25.3.6 Data or Biological Sample Repositories

A repository is a collection of data or biological specimens whose organizers:

- Receive data or specimens from multiple sources
- Maintain the data or specimens over time
• Control access to and use of data or specimens by multiple individuals and/or for multiple purposes, which may evolve over time

These policies and procedures apply to both data and biological sample repositories. For simplicity, both are referred to as samples. The CPHS Form: “Data, Specimens, Registry” Form assists with these determinations.

There are two types of repositories, non-research repositories and research repositories:

25.3.6.1 Non-research Repositories

Non-research repositories are created and maintained for purposes that are totally unrelated to research. Such purposes may include diagnosis, treatment, billing, marketing, quality control, and public health surveillance.

Even though these repositories are not created for research purposes, they may contain information that is of great interest to researchers. The creation (or operation) of non-research databases or repositories does not involve human subject research and does not require IRB oversight. However, IRB oversight is required for research of identifiable private information or identifiable human specimens from non-research databases and repositories (including data/tissue banks and registries).

• When research involves identifiable private information or identifiable human specimens each research use must receive prospective IRB review and approval and continuing IRB oversight as applicable.

• Researchers should submit an application for IRB review and receive IRB approval before initiating the research.

• The application should include any available information about the circumstances under which the information or specimens were originally collected.

• The IRB may require researchers to obtain informed consent of participants for research involving information or specimens contained in non-research databases or repositories. The IRB can waive the requirement for informed consent if the research meets the regulatory criteria for waiver.

25.3.6.2 Research Repositories

Research repositories are created and maintained specifically for research purposes. Such purposes may include databases to identify prospective participants, patient outcome information to evaluate treatment effectiveness, and tissues samples for future research.

Research repositories may involve three components:

• Sample collection;

• Sample storage and data management; and

• Use.
Sample collection

If the samples were collected for research purposes or are associated with information that can identify the donor, informed consent must be obtained from the donor unless appropriately waived by the IRB.

The consent document should include:

- A clear description of
  - the operation of the database;
  - the specific types of research to be conducted;
  - the conditions under which data is released to recipient-investigators; and
  - procedures for protecting the privacy of participants and maintaining the confidentiality of data
- A statement regarding future withdrawal of the data from the study (i.e., whether participants may, in the future, request that their data be destroyed or that all personal identifiers be removed from data).
- Other information, such as the length of time that data will be stored, participants' access to information learned from the research, and secondary uses of the samples should be considered as appropriate.

Repositories should have data submission policies to ensure that the data is collected in an ethical manner, with informed consent and IRB approval.

Sample Storage and Data Management

Repositories should have written policies on:

- Data and tissue submission requirements
  - Informed consent
  - IRB review
- Physical and procedural mechanisms for the secure receipt, storage, and transmission of information and specimens
- Policies on release of information and specimens, including:
  - Coding
  - Release of identifiers
  - Certificates of Confidentiality

Use

As applicable, recipient-investigators should have a written data use agreement with the repository. The data use agreement should specify under what conditions the data is being
released to the recipient-investigator(s). The terms under which the data is released determine whether the research requires IRB oversight.

25.3.6.3 IRB Oversight

Operation of a research repository and its data management center under the jurisdiction of Dartmouth is subject to oversight by the Dartmouth IRB. A proposal to establish a repository is submitted to the IRB using the Initial Application form, specifying the conditions under which data and specimens will be accepted and shared, and ensuring adequate provisions to protect the privacy of participants and maintain the confidentiality of data. The IRB also reviews and approves the sample collection protocol and informed consent document for distribution to sample collectors and their local IRBs.

25.3.6.4 HIPAA

PHI in a non-research repository may not be used or disclosed for research purposes without written authorization or a waiver of authorization or use of information that does not require authorization (e.g., de-identification). HIPAA applies to submission of PHI to a research repository and authorization is required when appropriate.

25.4 Certificate of Confidentiality (CoC)

Certificates of Confidentiality are issued by the National Institutes of Health (NIH) to protect identifiable research information from forced disclosure. They are intended to allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. A CoC does not protect against voluntary disclosures by the investigator, but those disclosures must be specified in the informed consent form. An investigator may not use the Certificate to withhold data if the participant consents in writing to the disclosure.

Generally, any research project that collects personally identifiable, sensitive information and that has been approved by an IRB operating under either an approved Federalwide Assurance issued by OHRP or the approval of the FDA is eligible for a Certificate. Federal funding is not a prerequisite for an NIH-issued Certificate, but the subject matter of the study must fall within a mission area of the National Institutes of Health, including its Institutes, Centers and the National Library of Medicine.

25.4.1 Statutory Basis for Protection

Protection against compelled disclosure of identifying information about participants in biomedical, behavioral, clinical, and other research is provided by the Public Health Service Act §301(d), 42 U.S.C. §241(d):

"The Secretary may authorize persons engaged in biomedical, behavioral, clinical, or other research (including research on mental health, including research on the use and effect of
alcohol and other psychoactive drugs) to protect the privacy of individuals who are the subject of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals."

25.4.2 Usage

Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for participants or damage their financial standing, employability, insurability, or reputation. By protecting investigators and institutions from being compelled to disclose information that would identify research participants, CoCs help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy.

Any investigator engaged in research in which sensitive information is gathered from human participants (or any person who intends to engage in such research) may apply for a CoC. Research can be considered "sensitive" if it involves the collection of:

1. Research on HIV, AIDS, and STDs;
2. Information about sexual attitudes, preferences, practices;
3. Information about personal use of alcohol, drugs, or other addictive products;
4. Information about illegal conduct;
5. Information that could damage an individual's financial standing, employability, or reputation within the community;
6. Information in a medical record that could lead to social stigmatization or discrimination; or
7. Information about psychological well-being or mental health.
8. Genetic studies, including those that collect and store biological samples for future use;

This list is not exhaustive.

In the consent process and form, investigators should tell research participants that a CoC is in effect. Participants should be given a fair and clear explanation of the protection that it affords, including the limitations and exceptions.

A CoC protects research participants from legally compelled disclosure of their identity. It does not restrict voluntary disclosures by participants or investigators.

For example, a CoC does not prevent investigators from voluntarily disclosing to appropriate authorities such matters as child abuse, threatened violence to self or others or from reporting a communicable disease. If investigators intend to make such disclosures, this should be clearly
stated during the consent process and in the consent form which research participants are asked to sign.

A Certificate of Confidentiality does not authorize the person to whom it is issued to refuse to reveal the name or other identifying characteristics of a research participant if:

1. The participant (or his or her legally authorized representative) gives consent, in writing, to the disclosure of such information;
2. Authorized personnel of the Department of Health and Human Services (DHHS) request such information for audit or program evaluation, or for investigation of DHHS grantees or contractors and their employees; or
3. Release of such information is required by the federal Food, Drug, and Cosmetic Act or regulations implementing that Act.

25.4.3 Application Procedures

Any person engaged in research collecting sensitive information from human research participants may apply for a Certificate of Confidentiality. For most research, Certificates are obtained from NIH. If NIH funds the research project, the investigator may apply through the funding Institute. However, even if the research is not supported with NIH funding, the investigator may apply for a Certificate through the NIH Institute or Center funding research in a scientific area similar to the project.

If the research is conducting a sensitive research project that is covered by the Agency for Healthcare Research and Quality (AHRQ) confidentiality statute (42 U.S.C. section 299a-1(c) entitled “Limitation on Use of Certain Information”) or the Department of Justice (DoJ) confidentiality statute (42USC section 3789g), then a CoC is not required.

If there is an Investigational New Drug Application (IND) or an Investigational Device Exemption (IDE), the sponsor can request a CoC from the FDA.

For more information, see the NIH Certificates of Confidentiality Kiosk (http://grants.nih.gov/grants/policy/coc/index.htm).

25.5 Mandatory Reporting

The New Hampshire statute requiring reporting of communicable diseases:
NH RSA 141-C http://www.gencourt.state.nh.us/rsa/html/X/141-C/141-C-mrg.htm

The administrative regulation with more information on what needs to be reported and how to report: He-P 300 http://www.gencourt.state.nh.us/rules/state_agencies/he-p300.html

Dartmouth policy requires the solicitation of informed consent from all adult research participants and, where appropriate, parental permission and assent from children involved as research participants. In situations where conditions of abuse or neglect might be revealed, mandated reporters should make themselves known as such to parents of children under age 18, to minor participants and to participants who are potential victims of abuse or neglect.
Investigators should consult these sources to determine if potential participants should be
advised of mandatory reporting requirements during the informed consent process.

25.6 Dartmouth Students and Employees as Research Participants

When Dartmouth students and/or employees are being recruited as potential research
participants, investigators must ensure that there are additional safeguards for these
participants. The voluntary nature of their participation must be primary and without undue
influence on their decision. Investigators must emphasize to participants that neither their
academic status, grades nor employment will be affected by their participation decision.

To minimize coercion, investigators should avoid, whenever possible, the use of their students
and employees in procedures which are neither therapeutic nor diagnostic. Investigators
should solicit student and employee participants through means such as bulletin board notices,
flyers, advertisements in newspapers, and announcements in classes or laboratories other than
their own. When entering a classroom to recruit students and conduct research, e.g.,
administer a survey, investigators should do so at the end of the class period to allow non-
participating students the option of leaving the classroom (unless other arrangements have
been made), thereby alleviating pressure to participate.

25.6.1 Human Subject Research and Course Projects

Learning how to conduct ethical human subject research is an important part of a student’s
educational experience. Research activities that are designed as part of a course requirement
for purposes of a learning experience only and not “designed to develop or contribute to
generalizable knowledge” may not require IRB review and approval if all of the following
conditions are true:

- Results of the project are viewed only by the course instructor and discussed within
  the classroom for teaching and learning purposes.
- Results of the project are not made public through presentation (outside of the
  classroom) and are not published in paper or electronic format (e.g., cannot be
  made available on the internet, cannot be published in a journal, etc.).
- Procedures involve no more than minimal risk.
- Vulnerable populations are not targeted (e.g., children under age 18, prisoners,
  persons who are cognitively impaired, etc.).
- Data collected are recorded in such a manner that participants are not identifiable
  (images in videotapes and photographs and voices on audiotape are not
  identifiable).
- When appropriate, informed consent is obtained.

25.6.1.1 Responsibility of the Course Instructor:

The course instructor is responsible for ensuring the protection of human subjects (including a
process is in place for obtaining voluntary consent from research participants when
appropriate), and for monitoring the students’ progress.
When designing a project, students should be instructed on the ethical conduct of research and on the preparation of the IRB application, when such is required. Instructors and students should:

- Understand the elements of informed consent;
- Develop appropriate consent documents;
- Plan appropriate strategies for recruitment;
- Identify and minimize potential risks to participants or others;
- Assess the risk-benefit ratio for the project;
- Establish and maintain strict guidelines for protecting privacy and confidentiality; and
- Allow sufficient time for IRB review, if applicable, and completion of the project.

In making a determination of whether or not a class research project requires IRB review, the instructor is encouraged to contact the IRB Office for assistance.

25.6.1.2 Individual Research Projects Conducted by Students

Independent study projects, senior theses, undergraduate research projects, Masters and advanced degree research, and similar exercises that meet the regulatory definition of human subjects’ research must be submitted for IRB review prior to the enrollment of participants or data collection. This includes human subject research activities that ultimately contribute to part or all of a thesis, dissertation, or other type of publication or presentation. IRB review/approval cannot occur after a study has begun.

Undergraduate students may not serve as principle investigators. A faculty member must be identified as the PI and is responsible for the conduct of the study.

Students, Advisors, Faculty Sponsors and Instructors should contact the IRB Office with any questions.

25.6.2 Independent Study, Theses and Dissertations

These research activities, including research done as part of a course of study, that meet the regulatory definition of human subjects research must be submitted for IRB review prior to the enrollment of participants or data collection. IRB approval cannot occur after a study has begun.

Undergraduate students may not serve as principle investigators. A faculty member must be identified as the PI and is responsible for the conduct of the study. Students, Advisors, Faculty Sponsors and Instructors should contact the IRB Office with any questions.
25.7 Oral History

A decision whether oral history or other activities solely consisting of open ended qualitative type interviews are subject to the policies and regulations outlined in an institution’s FWA and DHHS regulations for the protection of human research subjects (45 CFR 46) is based on the prospective intent of the investigator and the definition of "research" under DHHS regulations at 45 CFR 46.102(d): "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."

The evaluation of such activities hinges upon whether the activity involves a prospective research plan that incorporates data collection, including qualitative data, and data analysis to answer a research question; and the activity is designed to draw general conclusions or generalize findings.

In order to be subject to the Dartmouth human research protection policies, the activity must meet both of the above standards. This determination is made according to the procedures described in Section 5.

Investigators are advised to consult with the IRB Office regarding whether their oral history project requires IRB review.

25.8 Genetic Studies

Genetic research studies may create special risks to human participants and their relatives. These involve medical, psychosocial, legal and economic risks, such as the possible loss of privacy, insurability, and employability, change in immigration status and limits on education options, and may create a social stigma. Knowledge of one's genetic make-up may also affect one's knowledge of the disease risk status of family members. The CPHS “Genetic Form” addresses some of the following issues.

In studies involving genetic testing, several questions need to be addressed, including:

A description of any potential genetic results should be provided to participants in the consent form.
Will participants be given the option not to receive information?
Will participants be informed about any potential incidental genetic findings such as paternity and heritable conditions other than the one(s) under the study?

Describe the plan for sharing information, including interim or inconclusive research results, with participants, addressing the following:
What genetic information will they receive: interim results, final results, inconclusive results, incidental findings?
What is the meaning of the information for the participant?
What is the meaning of the information for the participant’s relatives and family members?

Describe the genetic counseling to be provided, addressing the following
What, if anything, is discussed as part of the consent process?
When, how, and where test or other research results will be communicated to participants?

Describe the clinical significance of the findings to participants
Does the investigator plan to disclose research findings to participants or their physicians for clinical use?
Are participants given a choice of whether this information is shared with their physician(s)?
Relatives and family members
Will participants be protected against disclosure of medical or other personal information about themselves to family members
If no, describe the information that will be disclosed and to whom it will be disclosed
Will relatives be invited to be participants based on genetic research results?
If yes, describe how they will be contacted and/or recruited

25.9 Case Reports Requiring IRB Review

In general, a case report on patients seen in one’s own practice and a comparison of these patients to existing reports in the literature does not constitute research under the purview of an IRB. If the intent of an intervention is designed to develop ‘generalized knowledge’ the project may be deemed to be research under the purview of the IRB. The IRB should be contacted prior to initiation if there are any questions.

25.9.1 Definitions

**Single Case Report:** The external reporting (e.g., publication, poster or oral presentation) of an interesting clinical situation or medical condition of a single patient. Case reports normally contain detailed information about an individual patient and may include demographic information and information on diagnosis, treatment, response to treatment, follow-up after treatment, as well as a discussion of existing relevant literature. The patient information used in the report must have been originally collected solely for non-research purposes as the result of a clinical experience. Please note although this does not constitute under the purview of the IRB, permission from the patient is strongly suggested especially if the identity of the individual may be determined.

**Case Series.** The external reporting (e.g., publication, poster or oral presentation) of an interesting clinical situation or medical condition in a series of patients (i.e., more than one patient). Case series usually contain detailed information about each patient and may include demographic information and information on diagnosis, treatment, response to treatment, follow-up after treatment, as well as a discussion of existing relevant literature. The information used in the report must have been originally collected solely for non-research purposes as the result of a clinical experience. Please note although this does not constitute under the purview of the IRB, permission from the patient is strongly suggested especially if the identity of the individual may be determined.
25.10 Research supported by the Department of Defense (DoD)

Research supported by the Department of Defense (DoD) is reviewed and conducted in compliance with part 219 of title 32 CFR, part 980 of title 10 USC, applicable parts of title 21 CFR (50, 56, 312, 600, 812), DoD Instruction 3216.02, DoD Directive 3210.07, and applicable additional requirements from respective DoD component(s).

A. Application and Scope

The following additional requirements apply to all biomedical and social/behavioral research involving human research participants conducted under the jurisdiction of Dartmouth when it:

- Conducts, reviews, approves, oversees, supports manages or otherwise is contractually subject to regulation by the DoD; and/or
- Human subject research performed under the jurisdiction of Dartmouth using DoD property, facilities, or assets.

In most cases, protocols covered by these requirements also will have review, approval and oversight by the DoD Human Research Protections Program.

Dartmouth assures that DoD supported research complies with all relevant DoD human subjects protection requirements, including but not limited to:

- The Belmont Report
- Title 21 Code of Federal Regulations 50, 56, 312, and 812, Food and Drug Administration (FDA) Regulations
- DoDD 3216.02, “Protection of Human Subjects and Adherence to Ethical Standards in DoD-supported Research”
- Title 10 United States Code Section 980 (10 USC 980), “Limitation on Use of Humans as Experimental Subjects”
- DoDD 3210.7, “Research Integrity and Misconduct”
- DoDD 6200.2, “Use of Investigational New Drugs in Force Health Protection”

B. Key Additional Requirements Not Covered by Title 45 CFR 46, Subparts B, C and D; 21 CFR 50, 56, 312, and 812

1. **Minimal Risk – [DoDI 316.02, enclosure 3, para 6b]**

The definition of minimal risk based on the phrase “ordinarily encountered in daily life or during the performance of routine physical or physiological examination or tests” shall not be interpreted to include the inherent risks certain categories of human subjects face in their everyday life. For example the risks imposed in research involving human subjects focused on a special population should not be evaluated against the inherent risks encountered in their work environment (e.g., emergency responder, pilot, soldier in a combat zone) or having a medical condition (e.g., frequent medical tests or constant pain.)

2. **Undue Influence – [DoDD 3216.2, enclosure 3, para 7e1]**

Service members shall follow their command policies regarding the requirement to obtain command permission to participate in research involving human subjects while on-duty and for approving off-duty employment or activities. Superiors (e.g., military and civilian supervisors, unit officers, and noncommissioned officers (NCOs)) are prohibited from influencing the decisions of their subordinates (e.g., junior enlisted personnel and equivalent civilians) regarding participation as subjects in research involving human subjects. Unit officers and senior NCOs in the chain of command shall not be present at the time of research subject solicitation and consent during any research recruitment sessions in which members of units under their command are afforded the opportunity to participate as research subjects. When applicable, officers and NCOs so excluded shall be afforded the opportunity to participate as research subjects in a separate recruitment session. During recruitment briefings to a unit where a percentage of the unit is being recruited to participate as a group, an ombudsman not connected in any way with the proposed research or the unit shall be present to monitor that the voluntary nature of individual participants is adequately stressed and that the information provided about the research is adequate and accurate.

3. **Education and Training – [DoDD 3216.2, enclosure 3, para 5]**

For initial and continuing research ethics education for all personnel who conduct, review, approve, oversee, support, or manage human participant research, there may be specific DoD educational requirements or certification required. The IRB shall use this guidance document as the basis for reviewing any DoD supported research and shall ensure that the PI has received this document before approving the research. The DoD component may evaluate the education policies to ensure the personnel are qualified to perform the research, based on the complexity and risk of the research.

4. **Appointment of a Research Monitor – [DoDI 3216.02, enclosure 3, para 8]**

- The IRB considers the appointment of a research monitor:
  - Required for research involving greater than minimal risk, although the IRB or organizational official can require this for a portion of the research or studies involving no more than minimal risk if appropriate.
  - The research monitor is appointed by name and shall be independent of the team conducting the research.
There may be more than one research monitor (e.g. if different skills or experience are needed.

The monitor may be an ombudsman or a member of the data safety monitoring board. The IRB must approve a written summary of the monitors’ duties, authorities, and responsibilities.

The IRB or HRPP official shall communication with research monitors to confirm their duties, authorities, and responsibilities.

The duties of the research monitor are determined on the basis of specific risks or concerns about the research.

- May perform oversight functions (e.g. observe recruitment, enrollment procedures, and the consent process, oversee study interventions and interactions, review monitoring plans and unanticipated problems involving risks to participants or others, oversee data matching, data collection and analysis).
- May discuss the research protocol with researchers, interview human subjects, and consult with others outside of the study.
- Report observations and findings to the IRB or a designated official.

The research monitor has the authority to:

- Stop a research study in progress.
- Remove individuals from study.
- Take any steps to protect the safety and well-being of participants until the IRB can assess.

Additional protections for pregnant women, prisoners, and children (Subparts B, C and D) of 45 CFR 46) – [DoDI 3216.02, enclosure 3 para 7]

Research involving pregnant women, prisoners, and children are subject to the DHHS Subparts B, C, and D.

- For purposes of applying Subpart B, the phrase “biomedical knowledge” shall be replaced with “generalizable knowledge.”
- The applicability of Subpart B is limited to research involving pregnant women as participants in research that is more than minimal risk and included interventions or invasive procedures to the woman or the fetus or involving fetuses or neonates as participants.
- Fetal research must comply with the US Code Title 42, Chapter 6A, Subchapter III, Part H, 289g.
- The exemption for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.
- Research involving a detainee as a human participants is prohibited.

Research involving prisoners cannot be reviewed by the expedited procedure.

When the IRB reviews research involving prisoners, at least one prisoner representative must be present for quorum.
• In addition to allowable categories of research on prisoners in Subpart C, epidemiological research is also allowable when:
  o The research describes the prevalence or incidence of a disease by identifying all cases or studies potential risk factor association for a disease.
  o The research presents no more than minimal risk
  o The research presents no more than an inconvenience to the participant.
• When a prisoner becomes a participant, if the researcher asserts to the IRB that it is in the best interest of the prisoner-participant to continue to participate in the research while a prisoner, the IRB Chair may determine that the prisoner-participant may continue to participate until the convened IRB can review this request to approve a change in the research protocol and until the organizational official and DoD Component office review the IRB’s approval to change the research protocol. Otherwise, the IRB Chair shall require that all research interactions and interventions with the prisoner-subject (including obtaining identifiable private information) cease until the convened IRB can review this request to approve a change in the research protocol. The convened IRB, upon receipt of notification that a previously enrolled human participant has become a prisoner, shall promptly re-review the research protocol to ensure that the rights and wellbeing of the human subject, now a prisoner, are not in jeopardy. The IRB should consult with a subject matter expert having the expertise of a prisoner representative if the IRB reviewing the research protocol does not have a prisoner representative. If the prisoner-participant can continue to consent to participate and is capable of meeting the research protocol requirements, the terms of the prisoner-participant’s confinement does not inhibit the ethical conduct of the research, and there are no other significant issues preventing the research involving human participants from continuing as approved, the convened IRB may approve a change in the study to allow this prisoner-participant to continue to participate in the research. This approval is limited to the individual prisoner-participant and does not allow recruitment of prisoners as participants.

6. Limitation of Waivers and Exceptions from Informed Consent - [DoDI 3216.02, enclosure 3 para 13; 10 U.S.C. 980]

If the research participant meets the definition of “experimental subject,” policies and procedure prohibit a waiver of the consent process unless a waiver is obtained from the Assistant Secretary of Defense for Research and Engineering. The Assistant Secretary of Defense for Research and Engineering may waive the requirements for consent when all of the following are met:
  o The research is necessarily to advance the development of a medical product for the Military Services.
  o The research may directly benefit the individual experimental subject.
  o The research is conducted in compliance with all other applicable laws and regulations.

Research involving a human being as an experimental subject is an activity, for research purposes, where there is an intervention or interaction with a human being for the primary
purpose of obtaining data regarding the effect of the intervention or interaction. If the research participant does not meet the definition of “experimental subject,” policies and procedure allow the IRB to waive the consent process.

For classified research, waivers of consent are prohibited.


The Dual Compensation Act prohibits an individual from receiving pay from more than one position for more than an aggregate of 40 hours of work in one calendar week. This prohibition applies to employees paid from either appropriated or non-appropriated funds, or a combination thereof, and includes temporary, part-time and intermittent appointments. This law if not applicable to enlisted off-duty military personnel in relation to their military duty.

When research involves U.S. military personnel, limitations on dual compensation include:

- Federal employees while on duty and non-Federal persons may be compensated for blood draws for research up to $50 for each blood draw.
- Non-Federal persons may be compensated for research participation other than blood draws in a reasonable amount, as approved by the IRB according to local prevailing rates and the nature of the research.
- Prohibit an individual from receiving pay of compensation for research during duty hours.
- U.S. military personnel may be compensated for research if the participant is involved in the research when not on duty.

8. **Requirement for Reporting - DoD 3216.02, enclosure 3 para 4(b)(4)**

The Institution shall promptly (no longer than within 30 days) notify the HRPO of the following: when significant changes to the research protocol are approved by the IRB, the results of the IRB continuing review, if the IRB used to review and approve the research changes to a different IRB, when the institution is notified by any Federal department or agency or national organization that any part of its HRPP is under investigation for cause involving a DoD-supported research protocol, and all UPIRTSOs, suspensions, terminations, and serious or continuing noncompliance regarding DoD-supported research involving human subjects.

9. **Recordkeeping Requirements - [DoDD 3216.2, para. 5.3.2; SECNAVINST 3900.39D, para. 8c(18)]**

Recordkeeping requirements for DOD-supported research with human subjects are longer than the Common Rule’s requirement. DOD may require submitting records to DOD for archiving.
Records maintained that document compliance or non-compliance with DoD requirements shall be made accessible for inspection and copying by representatives of the DoD at reasonable times and in a reasonable manner as determined by the supporting DoD component.

10. **Addressing and Reporting Allegations of Non-Compliance with Human Research Protections** - [DoDD 3216.2, para. 4.10; SECNAVINST 3900.39D, para. 8d(2) and 6k]

Report the initiation of all investigations and report results regardless of the findings to the Navy Secretary General and appropriate sponsors.

11. **Addressing and Reporting Allegations of Research Misconduct** - [DoDD 3216.2, para. 4.8; DODD 3210.7; SECNAVINST 3900.39D, para. 6l]

All findings of serious research misconduct under this section shall be reported to the Director, Defense Research and Engineering.

12. **Provisions for Research with Human Subjects using Investigational Test Articles (Drugs, Device and Biologics)** - [DoDD 3216.2, para 4.9; DoDD 6200.2; SECNAVINST 3900.39D, para. 6h]

Principal investigators may not be sponsors for INDs and IDEs.

13. **Prohibition of Research with Prisoners of War (POW) and Detainees** - [DoDD 3216.2, para 4.4.2; SECNAVINST 3900.39D, para. 6a (8)]

Research involving any person captured, detained, held or otherwise under the control of DoD personnel (military and civilian, or contractor employee) is prohibited.

14. **Classified research** [DoD l 3216.02, enclosure 3 para 13]

The involvement of classified information may be limited to information needed for IRB approval and oversight of the research; information needed to inform the human subjects during the consent process; and information provided by the human subjects during the course of the research. Secretary of Defense approval is required for all classified non-exempt research involving human subjects.

Informed consent procedures shall include:

(1) Identification of the Department of Defense as the supporting institution of the research, unless the research involves no more than minimal risk. The Secretary of Defense may grant an exception to this requirement on the grounds that providing this information could compromise intelligence sources or methods.

(2) A statement that the research involving human subjects is classified and an explanation of the impact of the classification.
The IRB shall determine whether potential human subjects need access to classified information to make a valid, informed consent decision.

IRB review shall be conducted using a full board review. Use of an expedited review procedure is prohibited.

15. Additional Requirements for DoD Sponsored Research

a) New research and substantive scientific amendments to approved research shall undergo scientific review and the review is considered by the IRB. The IRB may rely on outside experts to provide an evaluation of scientific merit.

b) When conducting research with international populations, additional safeguards for research conducted with international populations include: The Organization or Researcher has permission to conduct research in that country by certification or local ethics review and the Researcher follows all local laws, regulations, customs, and practices.

c) Disclosure regarding the provisions for research-related injury follow the requirements of the DoD component.

d) Surveys performed on Department of Defense personnel must be submitted, reviewed, and approved by the Department of Defense after the research protocol is reviewed and approved by the IRB.

e) When conducting multi-site research, a formal agreement between organizations is required to specify the roles and responsibilities of each party.

f) The following shall be promptly (no longer than within 30 days) reported to the DoD human research protection officer:
   a. When significant changes to the research protocol are approved by the IRB.
   b. The results of the IRB continuing review.
   c. Change of reviewing IRB.
   d. When the organization is notified by any Federal department, agency or national organization that any part of the HRPP is under investigation for cause involving a DoD-supported research protocol.

g) If consent is to be obtained from the research participant’s LAR, the research must intend to benefit the individual participant. The determination that research is intended to be beneficial to the individual research participant must be made by the IRB.

C. Responsibilities

It is the responsibility of the principal investigator to ensure compliance with all additional Department of Defense (DoD) requirements for human subject protection. It also is the responsibility of the IRB to ensure that all additional requirements by Department of Defense components for human subject protection have been met before IRB approval of the research project.