

Policies and Procedures for Human Research Protection

University Area Committee on the Use of Human Subjects in Research Harvard University

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1 Mission

The preamble to Harvard University's "Statement of Policies and Procedures Governing the Use of Human Subjects in Research" (voted by the President and Fellows of Harvard College on September 22, 2003) informs the oversight of all research covered by these policies and procedures:

Harvard University is guided by the ethical principles regarding research involving human subjects set forth in the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (*Ethical Principles and Guidelines for the Protection of Human Subjects of Research* [the "Belmont Report"]). The minimum standard is set by the Department of Health and Human Services [DHHS] regulations at 45 CFR 46 (the "Common Rule"). Harvard University has additional provisions beyond that standard, which help to establish the highest expectations for performance and oversight by investigators, Institutional Review Boards (IRBs), and the University.

The actions of Harvard University regarding research involving human subjects also must conform to all other applicable federal, state, and local laws and regulations.

To oversee and regulate research involving human subjects most effectively, the University maintains three Institutional Review Boards under the direction of the Office of the Provost, with three separate Federal Wide Assurances: one for the "University Area" (described more fully below); one for the Harvard Medical School and Harvard School of Dental Medicine; and one for the Harvard School of Public Health. Each of these three IRBs reviews research protocols involving human subjects and evaluates risk to subjects, protection against risks, and potential benefits likely to result from proposed research. It is the function of each IRB to 1) determine and certify that all projects reviewed by the IRB conform to policies and procedures set forth by the University's "Statement of Policies And Procedures Governing the Use of Human Subjects in Research," and, as appropriate, applicable regulations of the DHHS and the Food and Drug Administration (FDA) regarding the health, welfare, safety, rights, and privileges of human subjects; and 2) assist the investigator in complying with relevant federal, state, and local laws and regulations, and University policy. While the three IRBs operate independently, all participate in a University-wide Human Subjects Research Committee, established and run by the Office of the Provost.

1.1 Introduction

This document, ***Policies and Procedures for Human Research Protection – University Area, Committee on the Use of Human Subjects in Research, Harvard University***, describes the Human Research Protection Plan (HRPP), including the policies, procedures, and regulations governing research with human subjects and the requirements for submitting research proposals for the:

Faculty of Arts and Sciences; Harvard Graduate School of Education; John F. Kennedy School of Government; Harvard Divinity School; Harvard Business School; Harvard Law School; Harvard Graduate School of Design; and the Radcliffe Institute for Advanced Study (the "University-Area institutions").¹ This IRB will be referred to as the Committee on the Use of Human Subjects (CUHS), and is the IRB of record for the University Area. These policies and procedures apply to all research involving human subjects, regardless of sponsorship and performance site, conducted under the auspices of one or more University-Area institutions. A University-Area institution becomes "engaged" in human subjects research when its employees or agents (i) intervene or interact with living individuals for research purposes; or (ii) obtain individually identifiable private information for research purposes. For the purpose of determining engagement in human subjects research, "agents" include all individuals performing institutionally designated activities or exercising institutionally delegated authority or responsibility. The policies and procedures that follow are an implementation of the University-wide "Statement of Policies And Procedures Governing the Use of Human Subjects in Research" as voted by the President and Fellows of Harvard College, September 22, 2003 ("the Vote"), the preamble of which appears above.

All sites, domestic or foreign, engaged in research that is conducted by or in collaboration with any of the University Area institutions, will be obligated to conform to ethical principles that are at least equivalent to those cited in the previous paragraph or, when appropriate, as may be determined by the DHHS Secretary.

1.2 Ethical Principles: The Belmont Report

It is the duty of the CUHS to review and make decisions on all protocols for research involving human subjects. The primary responsibility of the CUHS is the protection of research subjects from undue risk and from deprivation of personal rights and dignity. This protection is best assured by consideration of **three principles**, which are the touchstones of ethical research involving human subjects:

- (1) that voluntary participation by the subjects, indicated by free and informed consent, is assured;
- (2) that an appropriate balance exists between the potential benefits of the research to the subject or to society and the risks assumed by the subject; and
- (3) that there are fair procedures and outcomes in the selection of research subjects and the potential distribution of likely benefits.

¹ As noted above, the policies and procedures set forth in this document do not cover the Harvard Medical School/Harvard School of Dental Medicine, or the Harvard School of Public Health, each of which has a separate IRB and human research protection plan.

These principles are summarized as **respect for persons, beneficence, and justice.**

Respect for Persons: Voluntary Participation and Informed Consent

One of the most important elements in any research involving human research subjects is the assurance of voluntary informed consent. Any person who is to be a research subject, whether the research is designed for his/her own direct benefit or for the advancement of scientific knowledge in general, must understand as completely as possible what is to be done and what the potential risks and benefits are. The person must give his/her consent freely, without pressure or inappropriate inducement. The CUHS strives to ensure voluntary informed consent of research subjects through careful review of the recruitment and consent process, including the consent form, information sheet, and/or oral consent script to be used with subjects.

The capacity for truly informed and voluntary participation in research varies widely among study populations. At one extreme, there may be ample understanding and manifest freedom from coercion; at the other, there may be degrees of understanding and freedom that affect the consent of potential subjects. The concept of informed consent extends to those studies in which the subjects are not able to give personal consent for themselves. In such cases the consent process and any documentation are addressed to those who have been designated responsible for the research subject's well being (e.g., parents of children). The CUHS's concern is to verify that the consent process and any consent documentation are likely to assist these persons in making an informed decision that is in the best interest of the research subject. The CUHS must exercise special care when considering subjects whose ability to give free and informed consent may be compromised in any way.

Beneficence: The Risk-Benefit Balance

The CUHS is charged with deciding, for any proposed activity that falls under its jurisdiction, whether "the risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant a decision to allow the subject to accept (those) risks" (Federal Register, May 30, 1974).

Assessment of the risk/benefit balance is a complex task. Risks of injury or discomfort to the individual may be physical, psychological, and/or social. Potential benefits may accrue to the individual, to a group to which the individual belongs, and/or to society. In reviewing applications, the CUHS must carefully assess not only the types and degrees of risks and benefits for the proposed subject population, but also the investigator's communication of these risks and benefits in the consent process and, where appropriate, the written consent form.

While the CUHS is not explicitly charged with reviewing scientific design, it must sometimes do so in order to weigh risk against benefit. If a study design seems unlikely to attain the stated aim of the investigation, then no benefit could be anticipated from conducting the study, and there is no justification for placing any research subject at risk. The design of the study must be sound, and the nature and likelihood of all risks and benefits must be made clear in any application to the CUHS.

Justice: The Fair Selection of Research Subjects

Both the risks and the potential benefits of research should be spread fairly among potential individual research subjects and research subject groups. Study design and selection of subjects should avoid bias against particular groups on the basis of race or national origin, ethnicity, gender, age, or social or socio-economic status.

Sharing Research Risks. The guiding principle in the ethical selection of research subject groups is that any risks of the research should fall upon the groups who might benefit from the research. If the results of a risky protocol might benefit the general population, it would be unethical to focus subject recruitment on vulnerable or disadvantaged groups (e.g., institutionalized people or prisoners; patients at free clinics primarily patronized by people unable to afford other medical care) simply because they are easily accessible or can be persuaded to participate. Nor should an undue share of research risks burden groups already burdened by other factors. Rather, attempts should be made to include a fair sampling of the populations who might benefit from the study. When research involves persons whose autonomy is compromised, it is expected that the research will relate to the conditions or circumstances of the research subject population. Whenever possible, groups fully able to consider research risks and informed consent should be asked to face research risks before more vulnerable populations. For example, investigational drugs are usually tested in adults before they are tested in children; some investigational drugs and procedures may be tested in healthy volunteers before being tested in patients.

Sharing Research Benefits. In recent years, increasing attention has been paid to the rights of various groups to be included in research. As individuals and through advocacy groups, many patients seek access to experimental treatments, believing that these experimental treatments may potentially provide the best medical care available. In addition, researchers, ethicists, and public officials have recognized that because many clinical trials focus primarily on white middle-class male research subject groups, the results of some trials may have been of questionable value for members of other social, racial, sexual, and ethnic groups. As a result, both the National Institutes of Health and the Food and Drug Administration now require that study design include as broad a range

of research subjects as feasible and the data be analyzed to uncover responses that differ between groups. For example, where women of child-bearing potential and pregnant and nursing women previously were routinely excluded from new drug trials, it is now required that whenever possible these women be asked to make their own choices after being fully informed of the risks of the research.

While most social and behavioral research does not, in general, directly benefit subjects in the same manner that clinical drug trials may, the principle of inclusion pertains.

2 Definitions

Human Subjects Research – For the purpose of this policy “human subject research” means any activity that either meets the DHHS definition of “research” and involves “human subjects” as defined by DHHS; or meets the FDA definition of “research” and involves “human subjects” as defined by the FDA. FDA-regulated studies, or aspects of a study, will be reviewed by other IRBs, see Section 15 below.

Research as defined by DHHS - a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition may be funded or unfunded, or may be conducted as a component of another program not usually considered research. For example, demonstration and service programs may include evaluation components that constitute research activities under this definition.

In addition, student research (i.e., projects conducted by student investigators who gather data about living individuals outside the class) that involves obtaining data in a systematic investigation (see definition of “systematic investigation” below) about living individuals through intervention or interaction with those individuals, or through the collection of their identifiable private information, are subject to review by the CUHS, even if the activities are not designed to develop or contribute to generalizable knowledge. See Section 16.5 for details on the procedures for CUHS review of student research.

Student research that is not designed to develop or contribute to generalizable knowledge is not considered “human subjects research” but is reviewed by the CUHS for ethical concerns as described in Section 16.5.

For the purposes of this policy, a “**systematic investigation**” is an activity that involves a prospective study plan that incorporates data collection (quantitative and/or qualitative; new data or existing) and data analysis to answer a research question. Investigations designed to develop or contribute to **generalizable knowledge** are those whose purpose is to generate data from which inferences may be drawn that would apply to individuals other than those participating in the

study, thus informing scholarly dialogue on topics related to the research subject, or related policy discourse.

Human subject as defined by DHHS - a living individual about whom an investigator (whether professional or student) conducting research obtains

1. data through intervention² or interaction³ with the individual, or
2. identifiable private information⁴.

Identifiable information as defined by DHHS - 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).

Research as defined by FDA regulations - means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act, or need not meet the requirements for prior submission to the 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

² Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

³ Interaction includes communication or interpersonal contact between investigator and subject.

⁴ Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is associated with the information or may readily be ascertained by the investigator) in order for obtaining the information to constitute research involving human subjects.

- effectiveness of a medical 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 Subject as defined by FDA regulations - means an individual who is or becomes a subject in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient. [21 CFR 50.3(g), 21 CFR 56.102(e)] A human subject includes an individual on whose specimen a medical device is used. [21 CFR 812.3(p)]

IRB - an Institutional Review Board established in accordance with and for the purposes expressed in this policy. The CUHS is the IRB of record for the University Area.

Minimal risk - 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.

Certification - the official notification by the institution to the supporting Department or Agency, in accordance with the requirements of this policy, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.

3 Institutional Authority

The President and Provost of Harvard University have designated the Associate Provost for Research Policy and Institutional Compliance as the officer who coordinates the University’s human research protections programs, reporting to the Provost, who serves as Institutional Official for the CUHS.

In accordance with the September 22, 2003 vote of the President and Fellows of Harvard College, the jurisdiction of the CUHS extends to ALL research (whether funded or not, and regardless of funding source) involving human subjects conducted by investigators under the auspices of the University-Area Institutions. Research under the auspices of the University-Area institutions includes research conducted by or under the direction of any employee or agent of the University-Area institutions (including students) in connection with his or her institutional responsibilities, conducted by or under the direction of any employee or agent of the University-Area institutions using any of their property or facilities or involving the use of these institutions’ non-public information to identify or contact human subjects for research purposes.

3.1 Assurance of Compliance

Harvard University holds a Federalwide Assurance (FWA), [FWA #00004837], applicable to all of the University-Area Institutions.

3.2 Committee on the Use of Human Subjects (CUHS) Office

The CUHS Office reports to the Dean of the Faculty of Arts and Sciences (since the CUHS is a Faculty of Arts and Sciences Standing Committee) and to the Harvard University Provost (who also serves as the Institutional Official and the Signatory Official on the Federalwide Assurance). The CUHS office is supervised by the Executive Officer of the CUHS. The Executive Officer has expert knowledge in regulatory issues regarding human subjects and, as the Human Protections Administrator, is the sole point of contact between the University-Area institutions and the Office for Human Research Protections, Department of Health and Human Services.

The CUHS is staffed by a sufficient number of administrative positions, including Research Officers and support staff, to perform its functions. The duties and responsibilities for all staff are found in their respective job descriptions, and their performance is evaluated on an annual basis, or more frequently as required, in accordance with the human resources policies and procedures of the Faculty of Arts and Sciences. CUHS Office Staff attend local and national conferences on human research protection issues and are expected to remain current on emerging issues regarding the use of human subjects in research.

3.3 Massachusetts Law

Harvard University and the CUHS rely on the Office of the General Counsel of the University to interpret and help apply Massachusetts law, where applicable to human subjects research.

4 Harvard University Institutional Review Boards

The University Area IRB, Medical School IRB, and School of Public Health IRB are administrative bodies established to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of this institution.

Harvard University's Provost reviews the activity of the three IRBs on a continuing basis so as to determine, in consultation with the Deans of the relevant Harvard faculties, the appropriate number of IRBs for the University.

4.1 Authority of the Committee on the Use of Human Subjects

The CUHS reviews and has the authority to approve, require modifications in, or disapprove all research activities conducted under the auspices of the University-Area institutions. The CUHS is required to ensure that the rights and welfare of

research subjects are appropriately safeguarded. In fulfilling these responsibilities, the CUHS reviews all the research documents and activities that bear directly on the rights and welfare of the subjects of proposed research, for example, the protocol, the consent/assent document(s), questionnaires or interview or survey instruments, and, for studies conducted under the Investigational New Drug (IND) regulations, the investigator's brochure. The CUHS must also review the methods and material that investigators propose to use to recruit subjects.

Before any human subject is involved in research in the University-Area institutions, the CUHS will give proper consideration to:

1. the risks to the subjects
2. the anticipated benefits to the subjects and to others
3. the importance of the knowledge that may reasonably be expected to result
4. the informed consent process to be employed

The CUHS has the authority to suspend, place restrictions on, or terminate approval of research activities that fall within its jurisdiction and that are not being conducted in accordance with its requirements or that have been associated with unexpected adverse events. The CUHS has the authority to observe or have a third party observe the consent process and the research if the CUHS determines that such observation is indicated.

4.2 CUHS Relationships

Although it may coordinate with other institutional regulatory committees, the CUHS functions independently. The CUHS's independent determination as to whether to approve or disapprove a protocol based upon whether or not human subjects are adequately protected may not be overruled except by a subsequent decision of the CUHS itself.

The University Human Subjects Research Committee (HSRC) meets regularly to ensure a dialogue is maintained among the various entities involved with human research protections at the University. HSRC membership is comprised of the chairs and staff of CUHS and the other two Harvard University IRBs, a Risk Management & Audit Services officer, and other institutional officials. An attorney from the Office of General Counsel advises the HSRC and representatives from some of the Harvard-affiliated teaching hospitals are regular guests. Currently the HSRC is chaired by a Professor at the Medical School. The committee acts in an advisory capacity to the Provost, monitoring the effectiveness of existing compliance programs, developing new or revised policies as changes in requirements occur, and disseminating updated compliance information to the research community.

Research that has been reviewed and approved by the CUHS may be subject to review and disapproval by officials of the relevant University Area institution.

However, those officials may NOT approve human subject research if it has NOT been approved by the CUHS.

If a CUHS chair, Officer, member, or staff person feels that the CUHS has been unduly influenced by any party, they shall make a confidential report to the Associate Provost for Research Policy and Institutional Compliance or to the Dean of the relevant institution. and/or the Dean of the Faculty of Arts and Sciences, depending on the circumstances, who shall investigate the allegations. Where warranted, corrective action will be taken to prevent additional occurrences.

Relationships with other institutions: Harvard University may choose, on a case-by-case basis, to provide human research protection oversight for another institution, or to delegate responsibility for human research protection oversight to another institution. In each case, a formal relationship must be established between the University and the other institution through either an Institutional Authorization Agreement or a Memorandum of Understanding. This relationship must be formalized before the University will accept any human research proposals from the other institution, or delegate responsibility for IRB review to another institution.

In the conduct of cooperative research projects, Harvard University acknowledges that each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with applicable federal regulations. When an Institutional Authorization Agreement exists, Harvard University may enter into a joint review arrangement, rely on the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort. When doing so, Harvard University will ensure that the review arrangement is approved, in writing, by the appropriate officials of the institutions involved, and the particular characteristics of its local research context are considered, either (i) through knowledge of its local research context by the relevant Harvard University IRB or (ii) through subsequent review by appropriate designated institutional officials, such as the Chair and/or other IRB members.

When a University Area institution is the coordinating center for a multi-center protocol, the CUHS will require the PI to ensure that IRB approval has been obtained at each participating site prior to initiation of the research at that site. At the time of initial review, the CUHS will assess the procedures for dissemination of protocol information (e.g., unanticipated problems involving risks to participants or others, protocol modifications, interim findings) to all participating research sites.

4.3 Roles and Responsibilities

4.3.1 Chair of the CUHS

The Dean of the Faculty of Arts and Sciences, in consultation with the Provost, and the CUHS Executive Officer, appoints a Chair of the CUHS to serve for renewable three-year terms. Any change in appointment, including reappointment or removal, requires written notification to OHRP.

The CUHS Chair should be a highly respected individual from within the University, fully capable of managing the CUHS and the matters brought before it with fairness and impartiality. The task of making the CUHS a respected part of the institutional community is the joint responsibility of the Chair and the Executive Officer. The CUHS must be perceived to be fair, impartial, and immune to pressure by the institution's administration, the investigators whose protocols are brought before it, and other professional and nonprofessional sources.

The CUHS Chair is responsible for conducting the meetings of the CUHS.

The CUHS Chair may designate the CUHS Officers and staff, and other CUHS members, to perform duties as appropriate including review, signature authority, and other CUHS functions.

The CUHS Chair, in consultation with the Executive Officer, advises the Institutional Official and the Dean of the Faculty of Arts and Sciences about IRB member performance and competence.

The performance of the CUHS Chair will be reviewed on an annual basis by the Institutional Official and the Dean of the Faculty of Arts and Sciences. If the Chair is not acting in accordance with the CUHS's mission, is not following these policies and procedures, has an undue number of absences, or is not fulfilling the responsibilities of the Chair, he/she will be replaced.

4.3.2 Acting Chair of the CUHS

The CUHS Chair, in consultation with the Executive Officer, may appoint another CUHS member to serve as Acting Chair of the CUHS in the absence of the Chair. The Acting Chair will have the same authority and duties as Chair and will be selected based on his/her qualifications and ability to fulfill the duties of Chair of the CUHS.

4.3.3 CUHS Executive Officer

The CUHS Executive Officer shall be qualified, by training and experience, to direct the administrative operation of the CUHS. S/he shall have a firm understanding of relevant regulations, law, and University policies that affect the conduct of research involving human subjects. The Executive Officer shall ensure the coordination of CUHS activities with other University academic and

administrative offices; s/he shall be responsible for presenting staffing and/or budgetary needs to School and University administration to ensure that the CUHS has access to sufficient resources to fulfill its obligations. Other duties and responsibilities of the Executive Officer are referenced throughout these Policies and Procedures.

The Executive Officer shall be a voting member of the CUHS, unless s/he has other responsibilities that could be viewed as presenting a conflict of interest (such as, administrative responsibilities relating to the review, submission, or administration of sponsored research proposals), in which case s/he shall be a non-voting member of the CUHS.

Since the CUHS is a Standing Committee of the Faculty of Arts and Sciences, appointment of the Executive Officer shall be made by the Dean of the Faculty of Arts and Sciences in consultation with the office of the Executive Dean and with the concurrence of the Institutional Official. The performance of the Executive Officer is reviewed on an annual basis by the office of the Executive Dean.

4.3.4 Subcommittees of the CUHS

The Chair and the Executive Officer of the CUHS, may designate a subcommittee of one or more other CUHS members to perform duties, as appropriate, including review, signature authority, and other CUHS functions.

Duties of a subcommittee may include the following:

1. Serve as designees by the CUHS Chair for the **expedited review** of new or continuing protocols, and/or modifications of continuing protocols. The subcommittee member(s) must be experienced, and must have expertise, acquired through education, training and/or experience on the CUHS, appropriate to the nature of protocols to be reviewed.
2. **Review and approve protocol revisions** where a protocol has been given provisional (“Contingent”) approval by the convened CUHS and the revisions are not substantive changes that are directly relevant to the determinations the committee must make to approve research, 45 CFR 46.111, see Section 8 below.
3. **Review allegations of noncompliance.** A subcommittee is appointed consisting of CUHS members (and non-members if appropriate) to review allegations of non-compliance. The subcommittee is given a charge by the CUHS, to determine whether the allegation has a basis in fact, and may do any or all of the following:
 - a. Review of protocol(s) in question;
 - b. Review of any relevant documentation, including consent documents, case report forms, subject's investigational and/or medical files, investigator's files, etc., as they relate to the investigator's execution of her/his study involving human subjects;

- c. Review of FDA audit report of the investigator, if appropriate;
 - d. Interview of appropriate personnel if necessary;
 - e. Preparation of either a written or oral report of the findings, which is presented to the full CUHS at its next meeting;
 - f. Recommend actions if appropriate.
4. Review findings of noncompliance. A subcommittee is appointed consisting of CUHS members (and non-members if appropriate) to review allegations of non-compliance. The subcommittee is given a charge by the CUHS to determine whether the finding of non-compliance is serious or continuing, and may do any or all of the following
- a. Review of protocol(s) in question;
 - b. Review of any relevant documentation, including consent documents, case report forms, subject's investigational and/or medical files, investigator's files, etc., as they relate to the investigator's execution of her/his study involving human subjects;
 - c. Review of FDA audit report of the investigator, if appropriate;
 - d. Interview of appropriate personnel if necessary;
 - e. Preparation of either a written or oral report of the findings, which is presented to the full CUHS at its next meeting;
 - f. Recommend actions if appropriate.
5. **Conduct on-site review.** Determination of the review interval and the need for additional supervision and/or participation is made by the CUHS on a protocol-by-protocol basis. For example, for an investigator who is performing particularly risky research, or for an investigator who has recently had a protocol suspended by the CUHS due to regulatory concerns, an on-site review by a CUHS subcommittee might occur, and/or approval might be subject to an audit of study performance after a few months of enrollment, or after enrollment of the first several subjects.

4.4 Resources for CUHS

The Dean of the Faculty of Arts and Sciences provides resources to the CUHS and CUHS Office, including adequate meeting and office space, and staff for conducting CUHS business. Office equipment and supplies, including technical support, furnishings, computers, printers, internet access, and fax and copy machines, plus books, journal subscriptions, and conference and training expenses are also made available to the CUHS and staff.

On a calendar-year basis, the CUHS reviews its direct personnel and non-personnel expenses and calculates the share of such expenses attributable to projects from each of the University-area institutions other than the Faculty of Arts and Sciences submitting proposals to the CUHS. Each institution is invoiced for its share of the expenses and the funds are reimbursed to the Faculty of Arts and Sciences. In addition, the office of the Provost provides support for some activities that benefit all HRPPs at the University. The resources provided for the

CUHS and CUHS office are reviewed each year during the annual budget process.

4.4.1 Annual Report

The CUHS summarizes its actions and operations in an Annual Report that is distributed to the Institutional Official and relevant University Area administrators. Following distribution of the Annual Report, the CUHS Executive Officer and Chair confer regarding the capacity of the organization to accomplish IRB reviews in a thorough and timely manner, and make recommendations to the Institutional Official about any changes they deem appropriate.

4.5 Conduct of Quality Assurance/Quality Improvement Activities for CUHS Operation

The HSRC will coordinate regular review of the activities of all IRBs and HRPPs at the University. (See Section 11 for a detailed discussion of investigations and audits.) CUHS staff will conduct investigations and reviews of ongoing research when the CUHS directs a review to be conducted or when a complaint or allegation of non-compliance is received and requires an investigation. In addition, the staff will conduct “not for cause” reviews of research.

5 CUHS Membership

5.1 Composition of the CUHS

1. The CUHS will have **at least five members** with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution.
2. The CUHS will be 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 CUHS will be able to ascertain the acceptability of proposed research in terms of institutional policies and regulations, applicable law, and standards of professional conduct and practice. The CUHS will therefore include persons knowledgeable in these areas. Because much of the research that the CUHS regularly reviews is grounded in social, behavioral, or educational disciplines, and the protocols occasionally involve a vulnerable category of subjects (e.g., children, prisoners, pregnant women, or handicapped or mentally disabled persons), consideration will be given to the inclusion of one or more individuals on the CUHS who are knowledgeable about and experienced in working with these subject populations.

4. Every nondiscriminatory effort will be made to **ensure that the CUHS does not consist entirely of men or entirely of women**, however, no membership selection shall be made to the CUHS solely on the basis of gender.
5. The CUHS will always include at least one member whose **primary concerns are in scientific areas** and at least one member whose **primary concerns are in nonscientific areas**. The CUHS shall not consist entirely of members of one profession.
6. The CUHS will always include at least one member who is **not otherwise affiliated with the institution** and who is not part of the immediate family of a person who is affiliated with the institution.
7. One member may satisfy more than one membership category.
8. The Officers of the CUHS may be voting IRB members, except that CUHS staff whose other University responsibilities include review and approval of sponsored proposals must serve as non-voting members.
9. A doctoral-level graduate student may serve as a voting member of the CUHS. A prospective graduate student member must have written approval from his/her graduate advisor to serve as a CUHS member and may ordinarily serve on the CUHS only for a two-year term.

5.2 Appointment of Members to the CUHS

The CUHS Chair, in consultation with CUHS staff, identifies a need for a new or replacement member, or alternate member. Suggestions for potential new members may be made by CUHS staff, the CUHS Chair, the Dean of the relevant school, or the Provost. Department Chairs, Deans of University-Area institutions, and others may also forward suggestions for new members.

The final decision to invite a new member is made by the CUHS Chair, the Executive Officer, and the Dean of FAS. An invitation to serve is forwarded by the Office of the Secretary of the Faculty of Arts and Sciences. The Provost and OHRP are advised of all changes to the membership.

Appointments are made for a renewable annual period of service. Any change in appointment, including reappointment or removal, requires written notification. Members may resign by written notification to the Chair.

On an annual basis, the CUHS Chair and Executive Officer review the membership and composition of the CUHS to determine if it continues to meet regulatory and institutional requirements.

Alternate members. The CUHS may, at the election of the Chair, Executive Officer, and Institutional Official, have alternate members. The appointment and function of alternate members is the same as that for primary CUHS members, and the alternate's expertise and perspective are comparable to those of the

primary member. The CUHS roster will identify the primary member(s) for whom each alternate member may substitute. The alternate member will not be counted as a voting member unless the primary member is absent. When an alternate member substitutes for a primary member, the alternate member will receive and review the same materials prior to the CUHS meeting that the primary member received or would have received. The CUHS minutes will document when an alternate member replaces a primary member.

5.3 Use of Consultants (Outside Reviewers)

The CUHS Chair or a CUHS Officer reviews agenda items in advance of the meeting and determines whether a consultant may be required for scientific or scholarly expertise, knowledge of the local context, representation of certain categories of subjects vulnerable to coercion or undue influence, or other expertise. If so, the CUHS Chair or a CUHS Officer will solicit individuals from the University or the community with competence in these special areas to assist in the review of issues or protocols that require scientific or scholarly expertise beyond or in addition to that available on the CUHS. The CUHS Officer will inform consultants of the CUHS conflict of interest policy (see 7.4.5) and consultants must confirm to the CUHS Officer that they do not have a conflict of interest prior to review. Individuals who have a conflicting interest or whose spouse or family members have a conflicting interest in the sponsor of the research will not be invited to provide consultation.

When the project is scheduled for full board review, the consultant's findings will be presented to the CUHS either in person or in summary by the CUHS staff. Consultants may attend the relevant portion of CUHS meetings to provide advice or to answer members' questions but may not participate in or observe the vote.

Ad hoc or informal consultations requested by individual members (rather than the full board) will be requested in a manner that respects the researcher's confidentiality and is in compliance with the CUHS conflict of interest policy (unless the question raised is generic enough to protect the identity of the particular PI and research protocol).

Summaries of information provided by consultants are maintained in the protocol application records and information provided by consultants at convened meetings is summarized in the minutes.

5.4 Duties of CUHS Members

The agenda, submission materials, protocols, proposed informed consent forms and other appropriate documents are distributed to members prior to the convened meetings at which the research is scheduled to be discussed. Members receive the materials at least five days before each meeting, to allow full participation in the review of each proposed project. CUHS members will treat the research proposals, protocols, and supporting data confidentially. All copies of the protocols and supporting documents provided to members are

returned at the conclusion of the review for destruction by CUHS staff or a professional shredding service.

5.5 Attendance Requirements

Members are expected to attend all scheduled CUHS meetings. A member who is unable to attend a scheduled meeting should inform the CUHS Chair or a CUHS Office staff member. If the inability to attend will be prolonged, a request for an alternate to be assigned may be submitted to the Chair or the Executive Officer.

5.6 Training / Ongoing Education of Chair and CUHS Members in Regulations, Procedures

A vital component of a comprehensive human research protection program is an education program for the CUHS Chair and the CUHS members. Harvard University is committed to providing training and an ongoing educational process for CUHS members and the staff of the CUHS Office, related to ethical concerns and regulatory and institutional requirements for the protection of human subjects.

Orientation

New CUHS members, including alternate members, will meet with the Chair, Executive Officer, and selected staff for an orientation session. At or before the session, the new member will be given a copy of the “CUHS Members’ Toolkit” (binder) that includes:

- Belmont Report;
- Federal regulations relevant to the business of the CUHS;
- University Area Policies and Procedures for Human Research Protection [this document];
- Institutional Review Board Member Handbook, Amdur;
- Other reference and supporting materials.

New members must complete the Initial Education requirement for CUHS members before they may serve as Primary Reviewer/Presenter.

Initial Education

CUHS members and Office staff must complete “HETHR – Harvard Ethics Training in Human Research,” Harvard University’s online training program developed specifically for training both investigators and IRB personnel.

In addition, CUHS Office staff will attend relevant professional development programs at the earliest opportunity, such as programs presented by PRIM&R. As part of their ongoing education, CUHS members will also be invited to attend PRIM&R conferences, or other educational opportunities.

Continuing Education

To ensure that oversight of human research is ethically grounded and the decisions made by the CUHS are consistent with current regulatory and policy requirements, training is continuous for CUHS members throughout their service on the CUHS. Educational activities include, but are not limited to;

- In-service training at CUHS meetings;
- Distribution of copies of *IRB: Ethics and Human Research*;
- Identification and dissemination to CUHS members by the Executive Officer and CUHS staff (by mail, email, or during convened meetings) of new information that might affect the human research protection program, including laws, regulations, policies, procedures, and emerging ethical and scientific issues;
- Unlimited access to the CUHS Office resource library.

The University will provide support for the Chair, CUHS staff, and as many members of the CUHS as possible to attend annual PRIM&R conferences on human research protections.

The CUHS professional staff will be encouraged to apply for the Certificate for IRB Professionals (CIP) and sit for the CIP qualifying examination.

5.7 Review of CUHS Members' Performance

The CUHS Members' performance will be reviewed on an annual basis by the Executive Officer, in consultation with the Chair and CUHS staff. Members who are not acting in accordance with the CUHS mission or policies and procedures or who have an undue number of absences will not be invited to continue their service on the Committee, and appropriate substitutes will be recommended for appointment by the Dean.

6 CUHS Records

The staff of the CUHS must prepare and maintain adequate documentation of the Committee's activities and copies of all items reviewed, including but not limited to any of the following:

- applications for approval of research;
- protocols;
- investigators' brochures and recruitment materials;
- scientific evaluations that accompany the proposals;
- approved consent documents;
- DHHS-approved sample consent documents and protocols;

- approved HIPAA Authorization documents, if separate from the informed consent documents;
- proposed amendments and the CUHS's action on each amendment;
- progress reports submitted by investigators;
- reports of injuries to subjects and serious and unexpected adverse events;
- documentation of protocol violations and actions taken by the CUHS in response;
- documentation of non-compliance with applicable regulations.
- For initial and continuing review of research by the expedited procedure:
 - The specific permissible category.
 - Description of action taken by the reviewer.
 - Any findings required under the regulations.
- For exemption determinations cited the specific category of exemption.
- Determinations required by the regulations and protocol-specific findings supporting those determinations for.
 - Waiver or alteration of the consent process.
 - Research involving pregnant women, fetuses, and neonates.
 - Research involving prisoners.
 - Research involving children.
- For each protocol's initial and continuing review, the frequency for the next continuing review

CUHS records must also include continuing review activities and copies of all relevant correspondence between the CUHS and investigators. If there are significant new findings relevant to subjects' participation in the research, they will be provided to subjects, maintained with the related research proposal and, when reviewed at a CUHS meeting, documented in the minutes.

6.1 Minutes of CUHS Meetings

Proceedings must be written and available for review by the members in advance of a subsequent scheduled CUHS meeting date. Once approved by the members at a subsequent CUHS meeting, the minutes may not be altered by anyone at the University. Minutes of CUHS meetings must contain sufficient detail to show:

1. The presence of a quorum throughout the meeting, including the presence of one member whose primary concerns are in a non-scientific area;
2. Attendance at the meetings, including those members or alternate members participating through videoconference or teleconference, and documentation that those attending through videoconferencing or teleconferencing received all pertinent material prior to the meeting and were able to actively and equally participate in all discussions;
3. Alternate members attending the meeting and for whom they are substituting;

4. Actions taken by the CUHS, including those involving full review;
5. Separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened CUHS;
6. Documentation that the research meets the required criteria [45 CFR 46.116(d)] 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 an informed consent, along with protocol-specific findings justifying each of those determinations;
7. Documentation that the research meets the required criteria [45 CFR 46.117(c)] when the requirements for documentation of consent are waived, along with protocol-specific findings justifying each of those determinations
8. When approving research that involves populations covered by Subparts B, C, or D of 45 CFR 46, the minutes will document the CUHS's findings regarding the determinations stated in the Subparts along with protocol-specific findings justifying each of those determinations, or the CUHS's agreement with the findings and justifications as presented by the investigator on CUHS forms.
9. The vote on actions, including the number of members voting for, against, and abstaining; changes in the number of members if they join, leave or rejoin the meeting shall be noted, along with the effect on the quorum, if any.
10. A note indicating that when a CUHS member has a real or potential conflict of interest (see Section 7.5.7.) relative to the proposal under consideration, that the CUHS member was not present during the deliberations (except to answer questions from other CUHS members) or voting on the proposal (and that the quorum was maintained);
11. The basis for requiring changes in or disapproving research and documentation of resolution of these issues when resolution occurs;
12. A written summary of the discussion of controverted issues and their resolution;
13. Review of additional safeguards to protect vulnerable populations if entered as study subjects when this is not otherwise documented in CUHS records;
14. The determination of the level of risk, if not recorded elsewhere in CUHS records;
15. The frequency of continuing review of each proposal, as determined by the CUHS, if not recorded elsewhere in CUHS records;
16. Documentation, as required by 45 CFR 164(i)(2), indicating the approval of a waiver or alteration of the HIPAA Authorization;

17. Key information provided by consultants (unless separately documented in a report provided by the consultant).
18. Justification of any deletion or substantive modification of information concerning risks or alternative procedures contained in a DHHS-approved sample consent document.

6.2 Membership Rosters

A membership list of CUHS members must be maintained and must identify members sufficiently to describe each member's chief anticipated contributions to CUHS deliberations. The list must contain information including a member's name, earned degrees, status as scientist (physician-scientist, other scientist, social/behavioral scientist, or non-scientist); voting status, status as chairperson; representative capacities in terms of whether the member is knowledgeable or experienced in working with specific vulnerable populations; affiliated or non-affiliated status (whether the member or an immediate family member of the member was affiliated with the organization); indications of experience sufficient to describe each member's chief anticipated contributions; employment or other relationship between each member and the organization; alternate status; the primary members or class of primary members for whom each alternate member could substitute.

The CUHS Office must keep the membership list current.

The CUHS Office must provide an updated CUHS membership list to the Office for Human Research Protections, Department of Health and Human Services, and to its Institutional Official, when there is a membership change.

6.3 Records Retention Requirements

The records described in this section will be stored securely in the CUHS Office and will be retained for at least three years; records relating to research that is conducted, shall be retained for at least three years after completion of the research. If a protocol is cancelled without subject enrollment, CUHS records are maintained for at least three years after cancellation. Permanent records of CUHS actions, including agendas and minutes, are retained according to the University's General Records Schedule.

All records must be accessible for inspection and copying by authorized representatives of the federal OHRP, the FDA, and other authorized entities at reasonable times and in a reasonable manner.

Any destruction of CUHS records will be carried out in a manner that ensures their security to the point of destruction.

6.4 Written Procedures and Guidelines

The University Area Policies and Procedures for Human Research Protection detail the policies and regulations governing research with human subjects and the requirements for submitting research proposals for review by the CUHS.

These policies and procedures also detail:

1. Written procedures that the CUHS must follow for: conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous CUHS review; ensuring prompt reporting to the CUHS of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which CUHS approval has already been given, may not be initiated without CUHS review and approval except when necessary to eliminate apparent immediate hazards to the subject.
2. Written procedures for ensuring prompt reporting to the CUHS, appropriate institutional officials, and the federal Department or Agency head of any unanticipated problems involving risks to subjects or others, or any serious or continuing noncompliance with 45 CFR 46 or the requirements or determinations of the CUHS suspension or termination of CUHS approval.

These policies and procedures contain the most current information for reference by investigators and their staff as they plan and carry out research; however, this is not a static document, and it should be read in conjunction with the University's September 22, 2003 Vote. These policies and procedures are subject to annual review and revision by the CUHS, in consultation with the Associate Provost for Research Policy and Institutional Compliance and University counsel.

The CUHS Office keeps the University Area 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, through campus electronic mailing lists, and through in-person training, education, and forum sessions. All relevant policies and procedures are available on the CUHS website and paper copies are made available upon request. See http://www.fas.harvard.edu/~research/hum_sub/.

7 CUHS Review Process

Investigators may not conduct research involving human subjects without review by the CUHS. Upon initial evaluation by the CUHS Office staff, studies may be found not to be human subjects research, see 7.1, or to be human subjects

research that is exempt from review, see 7.2, or that qualifies for expedited review, see 7.3. CUHS Office staff will examine applications that will be reviewed at convened committee meetings, see 7.4, and seek any additional information and documentation from investigators that may facilitate the convened committee's consideration of the application.

7.1 Human Subjects Research Determination

While it is not obligatory, an investigator may request that the CUHS make a determination as to whether a proposed study constitutes human subjects research. If the request is oral (by phone or in person), it is the investigator's responsibility to maintain documentation of the CUHS decision. An investigator submitting an inquiry by email or in other written form must include a sufficient description and documentation of the proposed research activity for the CUHS to come to an informed conclusion about whether the activity constitutes human subjects research. On an annual basis, the CUHS Executive Officer will designate committee members and CUHS Office staff to determine whether an activity is research involving human subjects. The CUHS will respond in writing to written submissions and will keep a copy of the submitted materials and determination letter/email on file in the CUHS Office.

7.2 Exempt Research.

Investigators may not decide for themselves that their own (or their students') research projects involving human subjects are exempt. Determining whether a project qualifies for exemption requires familiarity with the Common Rule's exemption categories listed at 45 CFR 46.101(b) [see below]. Furthermore, exempt human subjects research is subject to the ethical requirements of the Vote, see Appendix A, and the CUHS may require additional protections so the exempt project complies with the Vote. The CUHS Executive Officer will designate CUHS staff and committee members, and other qualified individuals, who may make exemption determinations.

Investigators can initiate a CUHS exemption review orally or in writing. CUHS may require, depending on the nature of the proposed project, submission of any or all of the following before making a decision:

1. A complete description of the proposed project,
2. All recruitment materials (e.g., letter of invitation, recruitment script, flyer),
3. Consent form (when appropriate),
4. HIPAA authorization, waiver of authorization, or de-identification form (when appropriate),
5. All surveys, questionnaires, instruments, interview scripts, etc., or drafts or outlines thereof,
6. Letter(s) of permission from each non-University site of performance or a statement of how permission will be obtained

7. Faculty sponsor approval, if the applicant is not qualified to act as a Principal Investigator

Investigators will be given feedback either by phone or email as to the qualification of the application for exempt status. Once review is completed, if the exemption application is approved a notice of exemption will be sent to the investigator. In preparing a notice of exemption, the reviewer will document the category of research permissible for exemption within which the activity falls using the HIRBERT exemption category checklist.

7.2.1 Categories of Research Permissible for Exemption

[45 CFR 46.101(b)]

Research activities in which the only involvement of human subjects is in one or more of the following categories will be deemed exempt, with the exception of research involving children or prisoners, as noted below:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as
 - a) research on regular and special education instructional strategies, or
 - b) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
 - a) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and
 - b) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' 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:
 - a) the human subjects are elected or appointed public officials or candidates for public office; or
 - b) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.
5. Research and demonstration projects which are conducted by or subject to the approval of Federal Department or Agency heads, and which are designed to study, evaluate, or otherwise examine:
 - a) Public benefit or service programs;
 - b) procedures for obtaining benefits or services under those programs;
 - c) possible changes in or alternatives to those programs or procedures; or
 - d) possible changes in methods or levels of payment for benefits or services under those programs.

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

6. Taste and food quality evaluation and consumer acceptance studies,
 - a) if wholesome foods without additives are consumed; or
 - b) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Exemption Eligibility Exceptions: Vulnerable Populations:

- Children: Exemption for research involving survey or interview procedures or observations of public behavior does NOT apply, except for research involving observations of public behavior when the investigator does not participate in the activities being observed. (See Section 10.1.1 for the definition of a child)
- Prisoners: **exemptions do NOT apply.** CUHS review is required.

Exemption Eligibility Exceptions: FDA Regulated Research, see Section 15

7.3 Expedited Review of Research

[45 CFR 46.110]

The CUHS may use the expedited review procedure to review either or both of the following:

1. some or all of the research appearing on the list established by the DHHS Secretary [reproduced below, at 7.3.1] and found by the reviewer(s) to involve no more than minimal risk,
2. minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

A minor change in previously approved research is one that, in the judgment of the CUHS reviewer, makes no substantial alteration in (i) the level of risk to subjects; (ii) the research design or methodology; (iii) the number of subjects enrolled in the research; (iv) the qualifications of the research team; (v) the facilities available to support safe conduct of the research; or (vi) any other part of the research that would otherwise warrant review of the proposed changes by the convened CUHS. In order to be a minor change to previously approved research all added procedures must involve no more than minimal risk to subjects and fall into categories (1)-(7) of research that can be reviewed using the expedited procedure, see 7.3.1.

Under an expedited review procedure, the review may be carried out by the CUHS Chair or by one or more experienced reviewers (e.g., a subcommittee of the CUHS) designated on an annual basis by the Chair and Executive Officer from among members of the Committee. For CUHS members to serve as designees to the Chair for expedited review, they must be experienced, defined as having expertise, acquired through education/training and experience, appropriate to the field of protocols to be reviewed.

The CUHS Chair will provide a list of experienced CUHS members who are approved to review research under the expedited review procedure to the CUHS Office, and from the list, staff will choose one reviewer for each application. The CUHS Chair may appoint a subcommittee of members to review an application under the expedited procedure and make a recommendation; in this case responsibility for the expedited review decision will rest with the CUHS Chair.

When reviewing research under an expedited review procedure, the CUHS Chair or designated member should receive and review all documentation that would normally be submitted for a full-board review, including the complete protocol. They should use the Informed Consent Checklist and the HIRBERT Expedited Review Checklist to determine that the regulatory criteria for use of such a review procedure are satisfied and to record the applicable category, when the research

is undergoing initial review, continuing review, or review of modifications using the expedited procedure.

In reviewing the research, the reviewers may exercise all of the authorities of the CUHS except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth below.

7.3.1 Categories of Research Eligible for Expedited Review

[63 FR 60364-60367, November 9, 1998]

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 subjects.

- The categories in this list apply regardless of the age of subjects, except as noted.
- The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
- The expedited review procedure may not be used for classified research involving human subjects.
- The standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--utilized by the IRB.

Research Categories one (1) through seven (7) pertain to 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 (defined by DHHS 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"), 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. [45 CFR 46.402(a)]

(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 gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing

or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for 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)(4). This listing refers only to research that is not exempt.]

(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.]

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

(a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; *or*

(b) where no subjects have been enrolled and no additional risks have been identified; *or*

(c) where the remaining research activities are limited to data analysis.

[Of note, category (8) identifies three situations in which research that is greater than minimal risk and has been initially reviewed by a convened IRB may undergo subsequent continuing review by the expedited review procedure.

For a multi-center protocol, an expedited review procedure may be used by the IRB at a particular site whenever the conditions of category (8)(a), (b), or (c) are satisfied for that site. However, with respect to category 8(b), while the criterion that "no subjects have been enrolled" is interpreted to mean that no subjects have ever been enrolled at a particular site, the criterion that "no additional risks have been identified" is interpreted to mean that neither the investigator nor the IRB at a particular site has identified any additional risks from any site or other relevant source.]

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

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

7.3.2 Informing the CUHS

All members of the CUHS will be apprised of all expedited review approvals by means of a monthly memorandum listing the investigators, protocol titles, and period of approval. Copies of the expedited review protocols will be made available for any optional review at the request of any CUHS member.

7.4 Convened CUHS Meetings

Except when an expedited review procedure is used, the CUHS must review non-exempt proposed research only at convened meetings at which a **quorum** (see below) is present.

7.4.1 Schedule of CUHS Meetings

The CUHS meets on a regular basis throughout the year, ordinarily at least monthly during the academic year. The schedule for the year's meetings is published in advance to allow investigators time to plan their submissions. *Ad hoc* meetings may be called at the discretion of the Chair or as business requires.

7.4.2 Quorum

A quorum consists of a simple majority of the voting membership, including at least one member whose primary concern is in a non-scientific area. The CUHS Chair, with the assistance of the staff, will confirm that an appropriate quorum is present before calling the meeting to order. The Chair will be responsible for ensuring that the meetings remain appropriately convened.

A quorum must be maintained for each vote to occur. If a quorum is not maintained, the proposal must be tabled or the meeting must be terminated. All members present at a convened meeting have full voting rights, except those designated as non-voting members, and except in the case of a conflict of interest (see below). In order for the research to be approved, it must receive the approval of a majority of those voting members present at the meeting.

It is strongly recommended that CUHS members be physically present at the meeting. If physical presence is not possible, one or more members may be considered present if participating through teleconferencing or videoconferencing. In this case the member(s) must have received all pertinent material 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 CUHS members but may not be counted as votes or to satisfy the quorum for convened meetings.

7.4.3 New Protocol Applications

Applications are screened by the CUHS staff for completeness and regulatory compliance prior to their placement on the agenda.

The Protocol Application must, at a minimum, include enough information for reviewers to make determinations based upon the **Criteria for IRB approval of Research** [45 CFR 46.111]. Each application must include or address the following, except where inapplicable due to the nature of the proposed research:

1. Title of the study
2. Purpose of the study
3. Sponsor of the study
4. Subject inclusion/exclusion criteria
5. Recruitment Procedures
6. Whether some or all subjects are likely to be vulnerable, and if so, the justification for use of any special/vulnerable subject populations and a description of additional safeguards included in the protocol to protect their rights and welfare.
7. Whether prospective subjects are vulnerable to coercion or undue influence
8. The importance of the knowledge that might reasonably be expected, i.e., the scientific or scholarly rationale
9. Study design (including, as needed, a discussion of the appropriateness of research methods)
10. Setting in which the research will be conducted
11. Description of procedures to be performed
12. The possible/potential risks to the subjects
13. Provisions for minimizing risks/managing adverse reactions

14. Provisions for monitoring the data to ensure the safety of subjects, where research involves more than minimal risk
15. The anticipated benefits of the research
16. Circumstances of the consent procedure
 - a. Setting
 - b. Subject autonomy concerns
 - c. Language difficulties
 - d. Vulnerable populations
 - e. Procedures for documenting informed consent
 - f. Obtaining assent from minors
 - g. Using witnesses and/or translators
 - h. The person who would conduct the consent interview
 - i. The person who would provide consent or permission
 - j. Any waiting period between informing the prospective subject and obtaining consent
 - k. Steps taken to minimize the possibility of coercion or undue influence
 - l. The language used by those obtaining consent
 - m. The language understood by the prospective subject or the legally authorized representative
17. Document and data storage
18. Compensation to subjects for their participation including the amount and timing of payments
19. Compensation for injured research subjects
20. Costs to subjects for their participation in the study
21. Costs to third-party payers because of subject's participation
22. Provisions for protection of subject's privacy
23. Description of the resources available to protect research subjects, including: supervision, number, training, and qualifications of staff, appropriate support services.
24. Protocol-specific conflict of interest information
25. Indication whether the research requires review by other University research compliance committees, or other external committees or entities (other IRBs, other institutions granting subject access, school authorities, etc.)
26. Assurances: The PI must certify that
 - a. the study has been adequately designed to protect the human subjects; and
 - b. the research does not present any conflict of interest for the PI or any other co-investigators, or, if a potential conflict exists, that the

research will not proceed until an acceptable management plan has been developed and implemented (See Section 7.5.7.1).

7.4.4 Pre-Meeting Distribution of Documents

The place and time of meeting is set forth on the agenda cover sheet distributed to all CUHS members.

The agenda, with review assignments, and all protocols and supporting documentation to be reviewed are provided to all CUHS members approximately five days prior to each meeting.

The CUHS staff assigns a Presenter from the members of the CUHS for all protocols requiring full CUHS review. Presenters are assigned protocols based on related expertise. When making Presenter assignments, CUHS staff takes into consideration the vulnerable populations involved in the research. If CUHS Staff cannot identify reviewers with appropriate expertise, the Chair or the Executive Officer may solicit one or more consultants from the University or the community with competence in the appropriate areas (see “Use of Consultants,” Section 5.3).

Before the meeting, each protocol application (including background information, project protocol, and informed consent) is carefully reviewed by the reviewing team.

For initial review all CUHS members receive the following documentation, as applicable and are expected to review this information in enough depth to be able to discuss the information at the convened meeting:

1. Complete Protocol Application form
2. Recruitment materials / subject information (including all surveys and questionnaires)
3. Proposed Consent / Parental Permission / Assent Form(s)
4. Measures, Surveys, Interviews
5. Debriefing sheets or scripts
6. Copies of additional relevant approvals (other IRBs, institutional approval, etc.)

In addition, for protocols supported by sponsored funds, at least one CUHS Officer will receive and review the grant/contract/cooperative agreement proposal, the DHHS-approved sample consent form, and the DHHS-approved protocol, when these exist.

For renewal applications, the presenter will receive and review the original application and the complete protocol including any protocol modifications previously approved by the CUHS. All CUHS members will receive a protocol summary and a status report on the progress of the research, in the renewal application.

For the review of modifications, all CUHS members will receive all modified documents and review them in enough depth to be able to discuss the information at the convened meeting.

All CUHS members will use the CUHS Protocol Review Cover Sheet as a guide to completing their review, including initial review, continuing review, and review of modifications.

The meeting agenda will set forth the presenter and review team for each protocol. The Chair and CUHS Officers will review all proposals on the agenda.

Note: Principal Investigators who do not write their own protocols and responses to the CUHS must recognize that they bear ultimate responsibility for all studies submitted on their behalf. The PI signature signifies that s/he has approved all material that is submitted to the CUHS for review.

At the meeting, any members with questions about the goals, design, study procedures, safety procedures, and qualifications of the investigators may inquire of the presenter or CUHS staff. The presenter should specifically address the Risk/Benefit Balance of the investigation and the adequacy of the consent form in conveying human subjects concerns. Problems identified by the presenter or by other CUHS members are discussed and suggestions for any necessary changes are agreed upon by the CUHS. These issues are considered in the vote to decide CUHS action. In addition to the presenter's presentation, there may be presentations by Investigators or consultants, and then the Chair will lead discussion by Committee members until the Committee is prepared to vote.

At the discretion of the Chair or CUHS staff, Principal Investigators may be invited to answer questions about their proposed or continuing research at the CUHS meeting, either in person or by telephone or videoconference.

7.4.5 CUHS Member Conflicts of Interest

A CUHS member is considered to have a conflicting interest when the CUHS member or an immediate family member (parent, sibling, spouse, or child) of the CUHS member:

1. Is the Principal Investigator, project director, faculty adviser, or other member of the research team;
2. Has a financial interest in NSF- or PHS-funded research with value that, when aggregated for immediate family, represents \$10,000 or greater, 5% or greater interest in any one entity, \$10,000/year or greater in compensation;
3. Has a financial interest in an entity involved in the research with a value that exceeds the specified threshold in the conflict of interest policy of the University and/or the relevant Harvard faculty; or has an ownership interest (equity or stock options) in an entity involved in the research of any amount

whose value could not be referenced to publicly traded prices or other measure of fair market value;

4. Has received or will receive any compensation that may be affected by the outcome of the study;
5. Has a proprietary interest in the research, meaning a property or other financial interest in the research including, but not limited to, a patent, trademark, copyright, or licensing agreement;
6. Is an executive or director of the agency or entity sponsoring the research or an agency or entity with a financial interest in the research; or
7. Any other situation where a CUHS member believes that another interest may conflict with his or her objective review of the protocol.

Except when requested by the CUHS to be present to provide information, CUHS members will absent themselves from the meeting room when the CUHS reviews research in which they have a conflicting interest. The Chair will allow for discussion after the conflicted member has recused him/herself. The absent member is not counted toward quorum and his/her absence during the discussion and vote on the protocol will be noted in the CUHS meeting minutes.

Before the first CUHS meeting of the academic year, a copy of Paragraph 7.4.5 will be distributed to each committee member, and CUHS will obtain and keep on file the members' acknowledgement that they received and read it. At the start of each meeting, the Chair or a CUHS Officer will ask committee members to disclose any potential conflict of interest with respect to the proposals on the agenda.

CUHS staff members are available to consult with investigators who are developing plans to conduct research involving human participants, to provide guidance regarding protection of participants and the CUHS application process. Where a Research Officer provides material input regarding study design before the investigator submits a Request for Approval, that Research Officer will not approve the application by expedited review. If the proposed research is reviewed by the convened committee, the Research Officer who has provided guidance in the development of the research plan will abstain.

If a Research Officer who is a voting member of the committee concludes that his/her experience working with an investigator would potentially bias consideration of an application, either favorably or unfavorably, the Research Officer should not approve the application on an expedited basis or vote on it at a convened committee meeting.

7.5 CUHS Review Process

7.5.1 Possible CUHS Actions Taken by Vote

Approved: The study is approved as submitted.

Contingent approval: The protocol and/or consent form require minor revisions, such as wording changes, that are not directly relevant to the determinations the committee must make to approve, see 45 CFR 46.111, Section 8 below. The needed revisions are agreed upon at the meeting. These revisions are presented to the Principal Investigator for incorporation. The CUHS Chair, a subcommittee of the CUHS, or a CUHS staff committee member may approve the study upon receipt and review of the revisions without further action by the CUHS.

Deferred: Substantive issues regarding the protocol and/or consent form must be addressed. This action is taken if substantial modification or clarification is required, or if insufficient information has been provided for the CUHS to judge the protocol application adequately (e.g., the risks and benefits cannot be assessed with the information provided). CUHS approval of the proposed research may not occur until the full Committee reviews all material submitted by the investigator, unless the investigator submits additional materials that make the revised project eligible for expedited review in its entirety.

If the application is deferred the following will occur:

1. The CUHS Office informs the investigator in writing of its decision, questions, and concerns.
2. The investigator's response is sent to the CUHS Office.
3. In order to receive approval for a deferred protocol, it must be submitted for full CUHS review at a subsequent, convened meeting unless the investigator's response makes the revised project eligible for expedited review. The CUHS Office provides the CUHS with the investigator's response, the revised protocol and the previously submitted protocol. The item is placed on the agenda for the following meeting.
4. The protocol application is given full CUHS review again.
5. The outcome of the CUHS deliberations is once again communicated to the investigator in writing.
6. The CUHS determination concerning the subsequent amended submission will be documented in the minutes of that meeting.

Not approved: Questions are of such significance that the CUHS feels approval of the study is unwarranted. The CUHS will provide the investigator a statement of the reasons for its decision and an opportunity to respond in person at a convened meeting or at a meeting with a subcommittee, or in writing. Subsequent approval will require full CUHS review unless the protocol is changed sufficiently that it is eligible for expedited review and approval; in such cases, the CUHS will be informed at the next scheduled meeting of the expedited approval.

Approval *pro tempore*: [45 CFR 46.118]

There are two circumstances in which the CUHS may grant approval required by a sponsoring agency without having reviewed all of the study procedures and consent documents: (1) where study procedures are to be developed during the course of the research, but IRB approval is required by the sponsoring agency; and (2) where the involvement of human subjects depends on the outcomes of work with animal subjects. Under either circumstance, the CUHS may grant approval without having reviewed the as-yet-undeveloped recruitment, consent, and intervention materials. However, if the proposal is funded, the Principal Investigator must request and receive CUHS approval before any human subjects may be recruited or involved in research (including pilot studies or pre-tests). Approval *pro tempore* is granted to satisfy sponsoring agency requirements or to allow investigators to have access to funding to begin aspects of the project that do not involve human subjects. See Section 7.12 for discussion of the integration of this process with the procedures at the Office for Sponsored Programs.

7.5.2 Determination of Risk

At the time of initial and continuing review, the CUHS will make a determination regarding the risks associated with the research protocols. Risks associated with the research will be classified as either “not greater than minimal” or “greater than minimal” based on the definition of minimal risk in the Common Rule, Sec. 46.102 (i) or, for those subjects who are prisoners, the definition at 46.303. The meeting minutes will reflect the Committee’s determination regarding risk levels.

7.5.3 Period of Approval

At the time of initial review and at continuing review, the CUHS will make a determination regarding the frequency of review of the research protocols. All protocols will be reviewed by the CUHS at intervals appropriate to the degree of risk but no less than once per year. In some circumstances, a shorter review interval (e.g., biannually, quarterly, or after accrual of a specific number of participants) may be required. The meeting minutes will reflect the CUHS’s determination regarding review frequency.

7.5.4 Review More Often Than Annually

Unless specifically waived by the CUHS, research that meets any of the following criteria will require review more often than annually:

1. Significant risk to research subjects (e.g., death, permanent or long lasting disability or morbidity, severe toxicity) without the possibility of direct benefit to the subjects;
2. The involvement of especially vulnerable populations likely to be subject to coercion (e.g., institutionalized psychiatric patients, incarcerated minors);
or

3. A history of serious or continuing non-compliance on the part of the Principal Investigator.

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

1. The probability and magnitude of anticipated risks to subjects.
2. The likely medical condition of the proposed subjects.
3. The overall qualifications of the Principal Investigator and other members of the research team.
4. The specific experience of the Principal Investigator and other members of the research team in conducting similar research.
5. The nature and frequency of adverse events observed in similar research at this and other institutions.
6. The novelty of the research making unanticipated adverse events more likely.
7. Any other factors that the CUHS deems relevant.

In specifying an approval period of less than one year, the CUHS may define the period with either a time interval or a maximum number of subjects either studied or enrolled. If a maximum number of subjects studied or enrolled is used to define the approval period, it is understood that the approval period in no case can exceed one year and that the number of subjects studied or enrolled determines the approval period only when that number of subjects is studied or enrolled in less than one year.

7.5.5 Independent Verification Regarding Material Changes

Protecting the rights and welfare of subjects sometimes requires that the CUHS verify independently, from sources other than the investigator, information about various aspects of the study. These include, but are not limited to, adverse event reporting, information in the scientific literature (including information about drug toxicity or other risks), and confirmation that no material changes occurred during the CUHS-designated approval period.

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

1. Protocols where concern about possible material changes occurring without CUHS approval have been raised based on information provided in continuing review reports or from other sources.
2. Protocols conducted by investigators who have previously failed to comply with Federal regulations and/or the requirements or determinations of the CUHS.
3. Protocols selected (systematically or at random) for post-approval review.

4. Whenever else the CUHS deems verification from outside sources is relevant.

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

1. The probability and magnitude of anticipated risks to subjects.
2. The likely medical condition, including mental health status, of the proposed subjects.
3. The probable nature and frequency of changes that may ordinarily be expected in the type of research proposed.

The CUHS may prospectively require that independent verification take place at predetermined intervals during the approval period, may retrospectively require such verification at the time of continuing review, or may require such verification at any time during the approval period in the light of new information.

7.5.6 Consent Monitoring

In reviewing the adequacy of informed consent procedures for proposed research, the CUHS may determine that special monitoring of the consent process by an impartial observer (a “consent monitor”) is required in order to reduce the possibility of coercion and undue influence, and to ensure that the informed consent process proceeds effectively and as described in the approved protocol.

Such monitoring may be warranted where the research presents significant risks to subjects, or if subjects are likely to have difficulty understanding the information to be provided. Monitoring may also be appropriate as a corrective action where the CUHS has identified problems associated with a particular investigator or a research project. Monitoring may also be performed on a not-for-cause basis as part of the CUHS Quality Assurance/Quality Improvement program.

When the CUHS deems it necessary to monitor consent, it will inform the investigator.

7.5.7 Conflicts of Interest

All Investigators and key research personnel must follow the Conflict of Interest Policy for their institution(s) as well as any applicable University policy. For the purposes of this section, “key research personnel” are those individuals who are responsible for the design, conduct, and/or reporting of study functions relating to human subjects, such as recruitment, obtaining consent, and recording data.

7.5.7.1 Protocol-Specific Conflict Management

The CUHS application requires that investigators certify that they have disclosed to the CUHS any actual, potential, or apparent conflict of interest for themselves, co-investigators, and key research personnel, and that no research will be carried out without a management plan for any conflict of interest. A conflict of interest is considered to exist if the investigator, co-investigator, or key research personnel, or any of their immediate family members (parent, sibling, spouse or child) has:

1. Has a financial interest in NSF- or PHS-funded research with value that, when aggregated for immediate family, represents \$10,000 or greater, 5% or greater interest in any one entity, \$10,000/year or greater in compensation;
2. A financial interest in an entity involved in the research with value that exceeds the specified monetary threshold in the conflict of interest policy of the University and/or the relevant Harvard faculty; or an ownership interest (equity or stock options) in an entity involved in the research of any amount whose value could not be referenced to publicly traded prices or other measure of fair market value;
3. Received or will receive compensation with value that may be affected by the outcome of the study;
4. A proprietary interest in the research, such as a patent, trademark, copyright, or licensing agreement;
5. Received or will receive payments from the sponsor that exceed the specified monetary threshold in the University Conflict of Interest Policy in one year;
6. Responsibility as an executive or director of the agency or entity sponsoring the research or an agency or entity with a financial interest in the research; or
7. A financial interest that requires disclosure per sponsor policy; or
8. Any other financial interest that the investigator believes may interfere with his or her ability to protect participants.

As part of its review process, the CUHS Executive Officer or Chair will obtain any conflict of interest disclosure the investigator has filed that relates to the research, and any conflict management plan that has been prepared. If the investigators application indicates that an actual or potential conflict of interest may exist, but has not previously been disclosed, the Executive Officer or Chair will obtain details from the investigator and make a determination as to whether any conflict that has been disclosed could adversely affect the protection of human subjects. If so, a conflict management plan will be developed by the CUHS Executive Officer and/or Chair, conferring as necessary with the Committee on Professional Conduct for FAS studies, or with the equivalent body at other University-Area institutions. Conflict of interest management plans will be

reviewed and approved by the convened committee and documented in the CUHS Minutes. If a conflict of interest exists, final CUHS approval cannot be given until a conflict management plan that adequately protects the human subjects in the protocol is in place.

7.5.7.2 Review of Proposed Conflict Management Plan

One or more CUHS Officers will review any proposed conflict management plan to determine if the conflict will adversely affect the protection of human subjects and if the management plan is adequate. Based on the significance of the conflict and the potential for adverse effects on the protection of subjects, conflict management plans can include:

- Disclosure to subjects through the consent process
- Modifications in the research plan
- Monitoring by independent reviewers
- Divestiture of financial interests
- Appointment of a non-conflicted investigator
- Prohibition of the conduct of the research at the University

The officer(s) reviewing the proposed conflict management plan can:

1. Accept the management plan and recommend approval to the CUHS
2. Recommend changes in the management plan
3. Refer the review to the Committee on Professional Conduct (for FAS investigators) or to the equivalent committee at the investigator's school. Any plan must ultimately be acceptable to the referring CUHS officer(s) and to the CUHS.

A copy of the final, approved conflict management plan will be filed with the relevant protocol(s) in the CUHS Office.

7.5.8 Other Committee Approvals

In the protocol application the investigator will be asked specific questions to determine if the research requires approval from other pertinent research compliance committees (Radiation Safety Committee, Committee on Microbiological Safety, IACUC, ESCRO, IRBs at other institutions, etc.). If the investigator answers yes to any of the questions, then documentation of approval from the other committees will be required. Final approval from the CUHS will be contingent on receipt of the required documentation.

7.5.9 Reporting CUHS Actions

The CUHS will notify investigators and, where appropriate, other interested parties, in writing, of its decision to approve or disapprove the proposed research activity or of modifications required to secure CUHS approval of the research activity.

For approved research:

1. The CUHS will send the Principal Investigator the “Report of Committee Action,” which is signed by a CUHS Officer.
2. **Certification (approval) letters** are signed by the CUHS Executive Officer or designated Research Officer.
3. Written **notification of approval** will include the following elements:
 - a. Name and affiliation of principal investigator;
 - b. Title of project as submitted to the CUHS
 - c. Funding source
 - d. Dates of CUHS approval
 - e. Notification of any fulfilled contingencies
 - f. Notice that **modifications** of approved projects must be reviewed and approved by the CUHS before they are initiated;
 - g. Notice that **adverse events/unanticipated problems** must be reported to the CUHS promptly and that the research may not proceed further until the CUHS has given permission.
 - h. Notice that approval of the protocol will **expire** on a date determined by the CUHS, unless renewed prior to that date. The period of approval will not exceed one year and there is no provision for a grace period after the expiration date. The deadline for submission of renewal materials is also specified.
4. For investigators who receive CUHS approval for applications sponsored by federal departments or agencies adopting the Common Rule [56FR28003, June 18, 1991], the CUHS Certification Memo will be provided to the investigator with a signed Protection of Human Subjects Assurance Identification / Certification / Declaration of Exemption form.

If the CUHS decides to disapprove a research activity, it will include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

The CUHS reports its findings and actions to the institution in the form of an Annual Report, which are distributed to the Institutional Official and relevant University Area Deans.

7.6 Continuing Review of Active Protocols (Renewals)

Approved research is subject to continuing CUHS review at least yearly, or more frequently if specified by the CUHS [45 CFR 46.109(e)]. For CUHS approval to remain current, this review must take place **before the approval expiration**

date. If continuing review is conducted earlier than 30 days prior to the approval expiration date (e.g., due to the scheduled CUHS meeting date), the protocol will be assigned a new approval date, that of the early continuing review. The approval expiration date will be based upon the new approval date for the purposes of future continuing reviews.

The approval date and the termination (expiration) date are clearly noted on all CUHS certifications sent to the PI and must be strictly adhered to. The expiration date is the last date that the protocol is approved. Investigators should allow sufficient time for development and review of renewal submissions.

To assist investigators the CUHS Office will send out renewal notices to investigators 75, 45, and 15 days in advance of the expiration date; 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, absent continuing review and approval, no extension to that date can be granted.

If approval lapses, subject enrollment and participation must stop, unless discontinuation of participation would be harmful to the subjects; see Section 7.6.4 below.

Research activities are subject to review and verification from sources other than the investigator that no material changes have occurred since the last CUHS approval.

7.6.1 Continuing review process

In accordance with DHHS regulations at 45 CFR 46.108(b) and at 46.115(a)(2), continuing review by the convened CUHS, with recorded vote on each study, is required unless the research is otherwise appropriate for expedited review under Section 46.110 (see below). Furthermore, DHHS regulations at 45 CFR 46.111 set forth the criteria that must be satisfied in order for the CUHS to approve research. These criteria include, among other things, determinations by the CUHS regarding risks, potential benefits, informed consent, and safeguards for human subjects. The CUHS must ensure that these criteria are satisfied at the time of both initial and continuing review

In conducting continuing review of research not eligible for expedited review, all **CUHS** members receive a copy of the renewal application, which includes the following information from the past year (cumulative data must also be included after the first renewal):

- the number of subjects enrolled;
- number of subjects who withdrew prematurely and reason(s) for their withdrawal, if known;
- the Description of Study;

- a summary of adverse events and any unanticipated problems involving risks to subjects or others and any withdrawal of subjects from the research or complaints about the research since the last CUHS review;
- any other relevant information, including information about risks associated with the research;
- a copy of the current informed consent document and any proposed changes.

Where appropriate (e.g., if the study involves treatment interventions and/or multi-site clinical trials) the investigator must also submit:

- summary of any relevant recent literature, interim findings, and amendments or modifications to the research since the last review;
- any relevant multi-center trial reports;
- a copy of the current HIPAA Authorization document, if any.

The assigned CUHS Officer receives a copy of the complete protocol including any modifications previously approved by the CUHS. Upon request, any CUHS member may have access to the complete CUHS protocol file and relevant CUHS minutes prior to or during the convened CUHS meeting.

When reviewing the current informed consent document(s), the CUHS should ensure the following:

- The currently approved or proposed consent document is still accurate and complete;
- Any significant new findings that may relate to the subject's willingness to continue participation are provided to the subject in accordance with DHHS regulations at 45 CFR 46.116(b)(5).

Review of currently approved or newly proposed consent documents must occur during the scheduled continuing review of research by the CUHS, but **informed consent documents should be reviewed whenever new information becomes available** that would require modification of information in the informed consent document.

7.6.2 Expedited Review at the time of Continuing Review

Generally, 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) at 63 FR 60364-60367, November 9, 1998 (see Expedited Review Categories). It is also possible that research activities that previously qualified for expedited review in accordance with 45 CFR 46.110, have changed or will change, such that an expedited continuing review would not be permitted.

7.6.3 Determining the Continuing Review Date

DHHS regulations at 45 CFR 46.108(b) and 109(e) require, respectively, that:

“... except when an expedited review procedure is used ... [the IRB must] review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas,” and

“...[an IRB must] conduct continuing review of research ... at intervals appropriate to the degree of risk, but not less than once per year.”

CUHS determination of the review interval and the need for additional supervision and/or participation is made on a protocol-by-protocol basis, as necessary to ensure the continued protection of the rights and welfare of research subjects. For example, for an investigator who is performing particularly risky research, or for an investigator who has recently had a protocol suspended by the CUHS due to regulatory concerns, an on-site review by a subcommittee of the CUHS 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 subjects.

Several scenarios for **determining the date of continuing review** apply to protocols reviewed by the CUHS at a convened meeting. The date by which continuing review must occur depends on the date of the convened meeting at which CUHS approval occurs. (These examples presume the CUHS has determined that it will conduct continuing review no sooner than within one year).

Scenario 1: The CUHS reviews and approves a protocol without any conditions at a convened meeting on October 1, 2002. Continuing review must occur within one year of the date of the meeting, that is, by midnight of the expiration date, September 30, 2003.

Scenario 2: The CUHS reviews a protocol at a convened meeting on October 1, 2002, and approves the protocol contingent on specific minor conditions the IRB chair or his/her designee can verify. On October 31, 2002, the CUHS chair or designee confirms that the required minor changes were made. Continuing review must occur within one year of the date of the convened CUHS meeting at which the CUHS reviewed and approved the protocol, that is, by midnight of the expiration date, September 30, 2003.

Scenario 3: The CUHS reviews a study at a convened meeting on October 1, 2002, and has serious concerns or lacks significant information that requires IRB review of the study at subsequent convened meetings on October 15 and October 29, 2002. At their October 29, 2002 meeting, the CUHS completes its review and approves the study. Continuing review must occur within one year of

the date of the convened meeting at which the CUHS reviewed and approved the protocol, that is, by midnight of the expiration date, October 28, 2003.

For a study approved under expedited review, continuing review must occur within one year of the date the CUHS Chair or designated CUHS member gives final approval to the protocol.

Review of a change in a protocol ordinarily does not alter the date by which continuing review must occur. This is because continuing review is review of the full protocol, 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 CUHS approval. Therefore, in order to avoid a lapse in approval, continuing review and re-approval of research must occur on or before midnight of the date when CUHS approval expires.

When continuing review occurs annually and the CUHS performs continuing review within 30 days before the CUHS approval period expires, the CUHS may retain the anniversary date as the date by which the continuing review must occur. This would be, for example, October 1, 2003, in the above Scenarios 1 and 2, and October 29, 2003, in Scenario 3, even if the continuing reviews took place up to 30 days prior to these dates.

7.6.4 Lapse in Continuing Review

The CUHS and investigators must plan ahead to meet required continuing review dates. If an investigator does not provide continuing review information to the CUHS or the CUHS has not reviewed and approved a research study by the end of the approval period specified by the CUHS, research activities must stop, including recruitment, advertisement, screening, enrollment, consent, interventions, interactions, data collection, and data analysis.

However, if the investigator is actively pursuing renewal with the CUHS and the CUHS Chair or Executive Officer believes that an over-riding safety concern or ethical issue is involved, the CUHS Chair or Executive Officer may permit already-enrolled subjects to continue their participation in the study for the brief time required to complete the review process.

As a courtesy, the CUHS Office will send out renewal notices via email 75, 45, and 15 days before the studies expire. However, it is ultimately the **investigator's responsibility** to initiate a renewal application, allowing sufficient time for the review and re-approval process to be completed before the current approval expires.

7.6.5 Studies that are Approved but Never Started

When the CUHS approves a study, continuing review should be performed at least annually. For the purposes of continuing review, the review date is

determined by the date of initial CUHS approval. Written progress reports should be received from the investigator for all studies that are in approved status prior to the date of expiration of CUHS approval. If subjects were never enrolled, and no new risks were identified, the investigator's progress report would be brief. Such studies may receive continuing review using expedited procedures [expedited category (8)(b)]. If the study is finally canceled without subject enrollment, records will be maintained for at least three years after cancellation [21 CFR 56.115(b)].

7.7 Changes to an Approved Protocol

Investigators may wish to modify or amend their approved applications during the period for which approval has been given. Investigators must seek CUHS approval before making changes unless the change is necessary to eliminate an immediate hazard to the subject (in which case the CUHS must then be notified at once).

Changes may be approved if they are within the scope of what the CUHS originally authorized. For example, if a researcher wishes to add a population to an existing study, but not alter the study procedures or purpose, a modification request is usually appropriate. Likewise, modifying a procedure without changing the study's purpose or study population may also be appropriate.

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

- Written request to modify protocol;
- Revised protocol application if changes are complex or involve multiple aspects or elements of the protocol;
- Revised approved consent/parental permission/assent documents (if applicable) or other documentation that would be provided to subjects when such information might relate to their willingness to continue to participate in the study;
- Revised or additional recruitment materials;
- Any other relevant documents.

CUHS Office staff will determine whether the proposed changes may be approved through an expedited review process or whether the changes warrant full board review.

7.7.1 Expedited review of Protocol Changes

The CUHS may use expedited review procedures to review minor changes in ongoing previously-approved research during the period for which approval is authorized [45 CFR 46.110; 63 FR 60364-60367, November 9, 1998 and 63 FR 60353-60356, November 9, 1998; 21 CFR 56.110(b)]. Research that was previously approved on an expedited basis may receive expedited review for

modifications that do not take the study out of the expedited review categories. An expedited review may be carried out by the CUHS Chair or by one or more qualified reviewers designated by the CUHS Chair and Executive Officer, see Section 7.3.

7.7.2 Full Board Review of Protocol Changes

When a proposed change in a research study is not minor (e.g., procedures involving increased risk or discomfort are to be added), then (1) the CUHS must review and approve the proposed change at a convened meeting before the change can be implemented, or (2) if the revised protocol will not involve greater than minimal risk and includes only procedures eligible for expedited review, a complete new application may be submitted for expedited review. The only exception is a change necessary to eliminate apparent immediate hazards to the research subjects [21 CFR 56.108(a)(4)]. In such a case, the CUHS should be promptly informed of the change following its implementation and should review the change to determine that it is consistent with ensuring the subjects' continued welfare.

When the CUHS reviews changes to previously approved research, the CUHS considers whether information about those changes might relate to participants' willingness to continue to take part in the research and, if so, whether to provide that information to participants.

7.8 Reporting Harm to Subjects and Unanticipated Problems

Research-related harm to subjects or others must be reported to the CUHS, except in the limited circumstances described below. In addition, investigators must report any research-related event or development that suggests that subjects or others face risks that are different or greater than those disclosed to participants in the consent process and described in the protocol application or renewal (an "Unanticipated Problem"). Harm should be considered "research-related" if participation in the research is known or suspected to have been a contributing factor in its occurrence.

Investigators must report serious harm or risk of serious harm immediately; other harm or Unanticipated Problems must be reported within 10 working days.

It is not necessary for investigators to report minor, transitory research-related harm to subjects that was specifically disclosed in the consent process and the protocol application or renewal, so long as it occurs no more frequently than anticipated.

Examples include:

- Subjects expressing frustration while completing commonly used questionnaires;

- Subjects expressing embarrassment or discomfort about answering personal questions in interviews or questionnaires;
- Subjects expressing upset and discontinuing participation in a study as a result of being shown disturbing photographs

Even when an investigator deems it unnecessary to promptly report minor, transitory harm to (or affronts to the rights and wellbeing of) subjects to the CUHS, if the investigator wishes to make changes to the protocol to eliminate or reduce the incidence of such occurrences, a request to amend the protocol should be submitted to the CUHS. Such occurrences should also be reported in any renewal application.

Not all Unanticipated Problems involve direct harm to subjects. New circumstances may arise that increase the risk of harm to subjects without directly harming them. Such events may present unanticipated risks to others (e.g., the sexual partners of the subjects, individuals the subject may come in contact with, family members, research personnel, etc.) in addition to the subjects.

While the event may not cause any detectable harm or adverse effect to subjects or others, it should be promptly reported to the CUHS. Examples of such events include:

- Any change to the protocol made without prior CUHS review to eliminate apparent immediate hazard to a research participant;
- Any deviation from the protocol (protocol violation) related to participant safety, significant new findings, a defined subset of adverse events, or IND safety reports;
- Any publication in the literature, safety monitoring report, interim result, or other finding that indicates an unexpected change to the risks or potential benefits of the research;
- Any complaint of a participant that indicates an unanticipated risk or that cannot be resolved by the research staff;
- Breach of confidentiality of research data;
- Breach of privacy/confidentiality/data security/loss of study data/destruction of study data due to noncompliance,
- Incorrect labeling/dosing of study medication or test article
- Any event that requires prompt reporting according to the sponsor.

An investigator's report to CUHS shall include the following information:

- (a) Appropriate identifying information, such as (i) the title of the research protocol; (ii) the Investigator's name; (iii) the CUHS protocol number; (iv) the name of the funding sponsor;

(b) A complete, detailed description of the event or development and the investigator's assessment of its significance for the risk profile of the study;

(c) A description of any actions that have been taken or proposed by the investigator, the study sponsor, the study coordinating site, and/or any other monitoring entity, in response to the event or development (e.g., suspension of new subject enrollment, modification of the research protocol, and/or modification of the informed consent information and/or process).

7.8.1 CUHS Review of Harm to Subjects and Unanticipated Problems

1) An unanticipated problem involving risks to subjects or others is defined as any problem that is (1) unforeseen and (2) indicates that subjects are at increased risk of harm.

2) The CUHS Chair in consultation with the Executive Officer reviews all reports and determines whether they represent an unanticipated problem involving risks to subjects or others as defined above.

3) If the CUHS Chair in consultation with the Executive Officer determines that the problem does not represent an unanticipated problem involving risks to subjects or others, no further action is taken under this policy.

4) If the CUHS Chair in consultation with the Executive Officer determines that the problem represents an unanticipated problem involving risks to subjects or others, the CUHS Chair in consultation with the Executive Officer determines whether the problem involves more than minimal risk to subjects or others.

5) If the CUHS Chair in consultation with the Executive Officer determines that the problem represents an unanticipated problem involving minimal risks to subjects or others, the CUHS Chair or other CUHS Officer may handle the problem or the problem may be reviewed by the convened IRB as described below for an unanticipated problem involving more than minimal risks to subjects or others.

6) All unanticipated problems involving more than minimal risks to subjects or others are reviewed by the convened IRB.

7) Following review of an unanticipated problem involving risks to subjects or others the problem is reported to the relevant regulatory agencies and institutional officials according to the procedures in Section 12.

Review of Unanticipated Problems Involving Risks to Subjects or Others by the Convened Committee

- 1) When the CUHS Chair in consultation with the Executive Officer place an unanticipated problem on the agenda of the convened committee, they will designate a member to present the matter, making their selection on the basis of familiarity with the protocol and any investigation of the problem. The CUHS Chair and Executive Officer may present the matter.
- 2) The entire CUHS file for the protocol will be made available to the presenter.
- 3) The presenter, in consultation with the CUHS Chair and the Executive Officer, will decide what documents will be provided to all committee members; at a minimum, the original application form and consent document will be provided.
- 4) The actions considered by the convened IRB:
 - a. Modification of the protocol.
 - b. Modification of the information disclosed during the consent process.
 - c. Providing additional information to past subjects.
 - d. Notification of current subjects when such information might relate to subjects' willingness to continue to take part in the research.
 - e. Requirement that current subjects re-consent to participation.
 - f. Modification of the continuing review schedule.
 - g. Monitoring of the research.
 - h. Monitoring of the consent process.
 - i. Suspension of the research.
 - j. Termination of the research.
 - k. Referral to other organizational entities.

7.9 Further Review/Approval of Human Subjects Research by Others within the Institution

While ordinarily there are no institutional reviews of human subjects protocols after the CUHS grants approval, in some cases research that has been approved by the CUHS may be subject to further review within the University. However, no one at Harvard may approve human subjects research if it has not been approved by the CUHS. [45 CFR 46.112]

7.10 Initiation of Research Projects

All research involving human subjects must be reviewed and approved by the CUHS prior to initiation of the research project. Approved research is subject to continuing review by the CUHS at least yearly, or more frequently if specified by the IRB [45 CFR 46.109(e)]. The date of continuing review will be based on the date of CUHS approval. [see Continuing Review, section 7.6, for further details.]

The effective date and the termination (expiration) date are clearly noted on all CUHS approval letters sent to the PI. Investigators must allow sufficient time for development and review of renewal submissions. By federal regulation, no extension to the expiration date can be granted.

Research activities are subject to internal audit and verification from sources other than the investigator that no material changes have occurred since the last CUHS review. The need to verify information independently will be determined by CUHS staff or by the CUHS at a convened meeting. The purpose of the verification will be to provide necessary protection to subjects when deemed appropriate by the CUHS.

The CUHS reserves the right to observe the consent process conducted under any research protocol and to inspect the records of investigators to ensure the protection of the human research subjects.

7.11 Appeal of CUHS Decisions

If a subcommittee of the CUHS makes a decision that the investigator believes will unduly restrict the proposed research, the investigator may request review at a convened CUHS meeting.

If the CUHS at a convened meeting makes a decision that the investigator believes will unduly restrict the proposed research, the investigator should first discuss the matter with the Chair or Executive Officer, taking care to explain the reasons why he or she believes that the proposed procedures comply with University policy and with federal regulations. If the issue cannot be resolved satisfactorily by negotiation, the investigator may appeal the decision of the CUHS in writing. The CUHS will consider the appeal based upon any new information provided and will continue to review a protocol as long as the investigator wishes to appeal; however, **no committee or entity other than the CUHS may reverse a decision made by the CUHS.**

7.12 Sponsored Research Grants, Contracts, and Cooperative Agreements

Sponsored awards will be reviewed by both the local University-Area School administration and the Office of Sponsored Programs (OSP) to determine if the award will include research involving human subjects. If the determination is affirmative, or if there is any question, the reviewers will consult with the CUHS office to determine whether the project will require determination of exemption by an individual other than the Principal Investigator, or will require submission of an application to the CUHS for review and approval.

If the proposed award will include activities that constitute research involving human subjects, the individual at OSP responsible for entering the project into the University's Grants Management Application Suite (GMAS) will check the field in GMAS indicating that human subjects are involved. No sponsored funds may be released for expenditure on the project until the CUHS has reviewed and approved, or until a determination of exemption is made. The date and period of

approval, or date of exemption determination, and any relevant comments, will be noted in GMAS.

Some sponsored awards (such as projects to develop and then administer a test procedure or instrument, or to test a procedure on animals before testing on humans) may include human subjects research procedures that will not begin until after the start of the award period. In such cases, the CUHS may grant "Approval *pro tempore*" (see section 7.5.1) to allow use of sponsored funding for support of activities prior to the involvement of human subjects. In consultation with the CUHS office and the Principal Investigator, an appropriate end date for the Approval *pro tempore* period will be entered in GMAS, and funds may not be expended on the award after that date without evidence that CUHS approval has been obtained or exemption determination has been granted. However, if project activities are continuing at a pace slower than anticipated, and the involvement of human subjects is still significantly distant, a new end date for Approval *pro tempore* may be assigned in GMAS, with the concurrence of CUHS staff.

8 Criteria for CUHS Approval of Research

As stated at 45 CFR 46.111, in order to approve research, the CUHS must determine that all of the following requirements are satisfied:

- (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 §46.116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §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.

8.1 Risk/Benefit Assessment

The goal of the assessment is to ensure that the risks to research subjects posed by participation in the research are justified by the anticipated benefits to the subjects and/or to society. Toward that end, the CUHS must:

1. judge whether the anticipated benefit, either of new knowledge or of improved health or welfare for the research subjects, justifies asking potential subjects to undertake the risks;
2. disapprove research in which the risks are judged unreasonable in relation to the anticipated benefits.

In assessing the risks and benefits of proposed research the CUHS must:

1. **identify the risks** associated with the research, as distinguished from the risks of therapies the subjects would receive, or the risks that the subject would experience in his/her everyday life, even if not participating in research;
2. **determine whether the risks will be minimized** to the extent possible;
3. **identify the probable benefits** to be derived from the research;
4. **determine whether the risks are reasonable in relation to the benefits** to subjects, if any, and assess the importance of the knowledge to be gained

8.1.1 Scientific Merit

In judging the benefits of the proposed research, in order to compare benefits to the risks posed to subjects the CUHS must determine that:

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

2. There is reason to expect that the research may answer, or contribute to knowledge about, the proposed question; and
3. The knowledge expected to result from the research is sufficiently important to justify any anticipated risk to subjects.

In making this determination, the CUHS will first consider the potential risks to subjects; scrutiny of scientific merit will increase in proportion to the degree of risk. In considering the question of scientific merit, the CUHS may draw on its own knowledge and disciplinary expertise, or on the knowledge and disciplinary expertise of others, such as reviews by a funding agency, or review by faculty or other experts, either within the University or outside. In the case of projects conducted by students or postdoctoral fellows under faculty supervision, the CUHS considers, in its review of scientific merit, that in approving an application, a faculty sponsor represents that s/he has reviewed the proposed procedures and is satisfied with the adequacy of the proposed research design.

8.2 Equitable selection of subjects

The CUHS will review the inclusion/exclusion criteria for the research to ensure equitable selection of subjects. In making this assessment the CUHS takes into account the purposes of the research and the setting in which the research will be conducted, and is particularly cognizant of the special problems of research involving populations that may be vulnerable to undue influence or coercion, such as children, prisoners, persons who are cognitively impaired, or persons who are economically or educationally disadvantaged (see Vulnerable Populations, Section 10).

8.2.1 Recruitment of Subjects

The CUHS will review all recruitment procedures, materials, and advertisements to ensure that they are consistent with the protocol, accurate, and non-coercive. The CUHS will review advertisements to ensure that they do not contain exculpatory language or unduly emphasize the amount subjects receive in compensation.

When examining advertisements, the CUHS will consider:

- The information contained in advertisements.
- The mode of their communication.
- The final copy of printed advertisements.
- The final audio/video taped advertisements.

When subjects are being paid, the CUHS will review both the amount of payment and the proposed method and timing of disbursement to assure that neither is coercive. Payment to subjects should not be considered a benefit of participation in assessing the proportionality of risk and benefit.

8.3 Informed Consent

The CUHS will ensure that informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by 45 CFR 46.116 and 21 CFR 50.20. In addition, the Committee will ensure that informed consent will be appropriately documented in accordance with and to the extent required by 45 CFR 46.117. See Section 9 below for detailed policies on informed consent.

8.4 Data Safety Monitoring

If research involves more than minimal risk, it must include adequate provisions to monitor data to ensure the safety of subjects.

If a protocol includes a data safety monitoring plan, the CUHS will review the data safety monitoring plan during initial review and at continuing review to determine that the protocol includes adequate provisions to monitor the data to ensure the safety of subjects.

8.5 Privacy and Confidentiality

The CUHS will determine whether a protocol design adequately **protects the privacy** of subjects and **maintains the confidentiality of the data**.

Definitions

Privacy - control of the extent, timing, and circumstances of sharing aspects of oneself (physical, behavioral, or intellectual) with others.

Confidentiality - prohibition against the improper disclosure of subjects' identity or information obtained by researchers.

Anonymity – total absence of means of identifying subjects.

Regulations

[45 CFR 46.102(f)] **Human subject** means a living individual about whom an investigator ... conducting research obtains

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

- **Private information** - information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (for example, a medical record).

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

The CUHS protects subjects' privacy interests by reviewing protocols to ensure that investigators do not gather unnecessary personal information and that data are not linked to subjects needlessly. Data should be stored securely, for no longer than needed for the purposes of the research. When future uses, such as teaching demonstration or publication are proposed, the CUHS will ensure that consent has been obtained, and that a plan has been made to retain only the data that is appropriate for the future use.

See Section 16.1 for detailed information regarding Certificates of Confidentiality.

8.6 Vulnerable Populations

The CUHS shall determine if appropriate **additional safeguards** are in place to protect the rights and welfare of subjects if they are likely to be members of a vulnerable population (e.g., persons with diminished autonomy). See Section 10 below for detailed policies on vulnerable populations.

9 Informed Consent

9.1 Informed Consent Process

No investigator may involve a human being as a subject in research without obtaining the legally effective informed consent of the subject or the subject's legally authorized representative unless a waiver of consent has been approved by the CUHS in accordance with Section 9.3 of this policy. In general, the CUHS considers individuals who are unable to give consent for their own clinical care to be unable to give consent for research participation. Tools or instruments such as the Mini Mental Exam also may be used to determine capability to consent.

The consent process must always:

- provide relevant information in language comprehensible to the prospective subject or representative;
- provide the prospective subject or representative sufficient opportunity to consider whether or not to participate; and
- minimize the possibility of coercion or undue influence.

The CUHS will consider where the consent process will take place and the individual who will be obtaining consent (e.g., the investigator, collaborator, or qualified designee) in determining the appropriateness of the consent process. When the timing, location, or status of the individuals participating in the proposed consent process may impair the potential participant's understanding of the research, the CUHS will require an alternative process.

No informed consent, whether oral or written, may include exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights.

A person knowledgeable about the consent process and the research to be conducted (i.e., a member of the project's research team) must obtain the informed consent.

If someone other than the investigator conducts the interview and obtains consent, the investigator needs to formally delegate this responsibility and the person so delegated must have received appropriate training to perform this activity.

9.2 Basic Elements of Informed Consent

Informed consent must be sought from each potential subject or the subject's legally authorized representative, in accordance with, and to the extent required by 45 CFR 46.116.

The basic elements of informed consent are:

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; a description of any reasonably foreseeable **risks** or discomforts to the subject;
2. a description of any **benefits** to the subject or to others which may reasonably be expected from the research;
3. a disclosure of appropriate **alternative procedures** or courses of treatment, if any, that might be advantageous to the subject;
4. a statement describing the extent, if any, to which **confidentiality** of records identifying the subject will be maintained;
5. for research involving more than minimal risk, an explanation as to the availability of medical treatment in the case of **research-related injury**, including who will pay for the treatment and whether other financial compensation is available;
6. 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;
7. a statement that participation is **voluntary**, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled;

8. for **FDA-regulated studies**, the possibility that the Food and Drug Administration may inspect the records needs to be included in the statement regarding subject confidentiality.

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) that 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 that may relate to the subject's willingness to continue participation must be provided to the subject;
6. the approximate number of subjects involved in the study.

9.3 Waiver of Informed Consent

There are two sets of circumstances in which the CUHS may either approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent set forth above, or may waive the requirement for informed consent entirely.

In the first circumstance, the CUHS must find and document that:

1. the research involves no more than minimal risk to the subjects;
2. the waiver or alteration will not adversely affect the rights and welfare of the subjects;
3. the research could not practicably be carried out without the waiver or alteration;

and

4. whenever appropriate, the subjects must be provided with additional pertinent information after participation.

In the second circumstance, the CUHS must find and document that:

1. 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:
 - a. public benefit or service programs;

- b. procedures for obtaining benefits or services under those programs;
- c. possible changes in or alternatives to those programs or procedures; or
- d. possible changes in methods or levels of payment for benefits or services under those programs;

and

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

9.4 Documentation of Informed Consent (Signed Consent)

Informed consent must be appropriately documented in accordance with, and to the extent required by, 45 CFR 46.117.

- 1. Informed consent is documented by the use of a written consent form approved by the CUHS and signed and dated by the subject and/or the subject's legally authorized representative at the time of consent.
- 2. A copy of the signed and dated consent form must be given to the person signing the form.
- 3. The consent form may be either of the following:
 - a. a **written consent document** that embodies the elements of informed consent, and that may be read to the subject and/or the subject's legally authorized representative, in which case the subject or representative must be given adequate opportunity to read it before it is signed; or
 - b. a **short form written consent document** stating that the elements of informed consent have been presented orally to the subject and/or the subject's legally authorized representative.

When this method is used, all of the following must be true:

- 1) there must be a witness to the oral presentation;
- 2) the CUHS must approve a written summary of what is to be signed by the subject or representative;
- 3) the witness must sign both the short form and a copy of the summary;
- 4) the person actually obtaining consent must sign a copy of the summary; and
- 5) copies of both the short form and the summary must be given to the subject or representative.

9.5 Waiver of Documentation of Informed Consent (Waiver of Signed Consent)

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

- 1) the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or
- 2) the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

When the CUHS considers waiving the requirement to obtain written documentation of the consent process, the CUHS must review a written description of the information that will be provided to subjects.

In cases in which the documentation requirement is waived, the CUHS will consider whether to require the investigator to provide subjects with a written statement regarding the research.

9.6 Review and Approval of the Informed Consent Form

The CUHS is responsible for the review and approval of the informed consent form submitted by the investigator. The wording on the informed consent form must contain all required elements and must meet all other requirements as described in this section. CUHS approval of the wording of the consent must be documented through the use of a certification stamp on each page that indicates the date of the most recent CUHS approval of the document and the expiration date. If the consent form is amended during the protocol approval period, the form must bear the approval date of the amendment rather than the date of the approved protocol.

When applicable, the CUHS needs to ensure that the required language for a valid authorization to release health information is included in separate HIPAA (Health Insurance Portability and Accountability Act) Authorization form. The CUHS may waive the requirement for an authorization or may alter the form or content of the authorization only in accordance with and as permitted by the HIPAA Privacy Rule (45 CFR 164.508). Such actions and the justification for them must be fully documented in the minutes of the CUHS meeting where the action was taken or reported (if approved by expedited review).

9.7 Consent and Language Barriers

Researchers should prepare both English language and translated consent forms for proposals that include non-English-speaking subjects. The CUHS may

consult with language experts or require a "back-translation" into English. In such cases, the investigator may be asked to provide documentation to verify the accuracy of the translation and back-translation.

If a non-English-speaking subject is enrolled unexpectedly, the subject cannot be enrolled until the CUHS has reviewed and approved the consent process and the process for documentation of consent.

In studies where written consent is indicated, and a potential subject understands English but does not read or write English, an impartial witness should document that the subject understands the research and the consent process and has consented to participate.

9.8 Parental Permission and Assent

See Section 10.1 for policies on parental permission and assent in research involving children.

9.9 Surrogate Consent

See Section 10.4 for policies on permission and assent in research involving adults with impaired decision-making capacity.

10 Vulnerable Populations

10.1 Research Involving Children

Research involving children is governed by 45 CFR 46, Subpart D.

10.1.1 Federal Definitions under 45 CFR 46

Children - 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.

Assent - a child's affirmative agreement to participate in research. Mere failure to object, absent affirmative agreement, should not be construed as assent.

Permission - the agreement of parent(s) or legal guardian to the participation of their child or ward in research.

Parent - a child's biological or adoptive parent.

Guardian - an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care.

10.1.2 Massachusetts Law

Age of majority. Eighteen is the age of majority both in Massachusetts (M.G.L. c. 231, § 85P) and under federal policy. When a person turns 18, s/he is considered to be an adult under the law.

Massachusetts law recognizes two instances when teenagers under the age of 18 may have the legal capacity to consent to medical treatment. These are the **emancipated minor** and **mature minor** rules. Note that these rules concern individuals in their capacity as **patients**, not as subjects in research, and also that they apply only to persons in Massachusetts. These rules would not apply, for example, to research subjects living in a foreign country, although that country might have analogous rules

Emancipated minor. A patient under 18 years of age may consent to treatment of any kind, except abortion, and may authorize the release of his or her medical records if he or she is: (a) married/widowed/divorced, a parent, (b) a member of the armed forces, (c) living apart from parents and managing his or her own finances, or, in the case of a female, (d) pregnant or believes herself to be pregnant. M.G.L. c. 112 § 12F. A female under the age of 18 may consent to an abortion if she is or has been married. Otherwise, consent must be obtained from her parent(s) or the procedure must be authorized by court order. M.G.L. c. 112 § 12S. Further, patients under 18 years of age may consent to treatment and may authorize the release of their medical records relating to: diseases dangerous to the public health, drug dependency (but not alcohol dependency), and pregnancy (but not abortion, except in the case of those who had married).

Mature minor. Under Massachusetts case law, students under the age of 18 who are not emancipated under M.G.L. c. 112, § 12F, can, in certain circumstances, nevertheless consent to treatment and control access to their medical records. In such cases, the clinician proposing to provide the treatment may determine that the patient is a mature minor capable of consenting to treatment. To reach this determination, the clinician must conclude that the minor is capable of giving informed consent to the treatment; and that it is in the best interest of the minor not to notify his or her parents of the intended medical treatment. In general, where a minor has the capacity to consent to medical treatment, that minor also has the capacity to control his or her medical records, including releasing them to others, such as researchers. In addition, there is an argument that a minor who has the capacity to consent to medical treatment also should have the capacity to consent to research that may accompany that treatment. However, this argument has not been tested in a Massachusetts court.

Parents or Guardians of minor children. In general, and as more fully explained below, parents and guardians may provide consent to participation in research for their children or wards. The definition of who is a parent or guardian differs in some respects under federal and Massachusetts laws. The

Massachusetts Uniform Statutory Will Act (the “Will Act”) indirectly defines “parent” in its definition of “child.” See M.G.L. c. 191B, § 1(1). Under this law, the “parent” is the biological or adoptive mother or father of a child. However, a father of a child who is not married to the child’s mother may not always be considered a parent; his status would depend on whether he openly treats the child as his offspring or on whether a court has made a paternity determination. Under the Will Act, the term “parent” does not include step-parents who have not formally adopted the child, foster parents, grandparents or other relatives. Id. In general, the term “guardian” is widely understood to mean a person lawfully invested with the power, and charged with the duty, of taking care of and managing the property and rights of someone who is considered incapable of administering his or her own affairs. This definition includes a person who legally has responsibility for the care and management of the person or estate or both of a child during his or her minority. Parents are usually considered the guardians of their children under Massachusetts law. For example, with respect to children, the Department of Mental Retardation defines “guardian” in its regulations concerning research as “a natural or adoptive parent, or the individual or agency with legal guardianship of the person.” 115 CMR 10.02. In order for a non-parent to grant permission for a child to take part in research, the person has to meet the definition of “guardian” as defined by DHHS regulations; individuals who meet the “widely understood term guardian” cannot grant permission for a child to take part in research, unless the person also meets the definition of “guardian” as defined by DHHS regulations.

Legal guardianship in Massachusetts usually is created through a court process, most often through the Probate Court, M.G.L. c. 201 § 2, although parents may designate another adult to be a guardian without having to invoke a court proceeding. This kind of guardian, once appointed, is also referred to as a “standby proxy,” whose authority becomes enforceable when the parent dies, becomes incapacitated or is unavailable to care for the child. M.G.L. c. 201 §§ 2B – 2D. The Department of Social Services or other state agencies may become the legal guardian of children it takes into custody. Legal guardians acting with authority pursuant to M.G.L. c. 201 §§ 2, 2B – 2D may consent on behalf of a child to general medical care, and so meet the DHHS definition of “guardian.”

In general, a parent or legal guardian is considered under federal policy to be the Legally Authorized Representative (“LAR”) of a child, and thus may consent to the child’s participation in a research project. Thus, for a child subject in research, a parent or guardian acting as an LAR can give permission (consent) on behalf of the child to participate in research. As discussed above, an exception to this general rule is where the research involves medical treatment and the child has the capacity to consent under the emancipated minor or mature minor rules.

When research that involves children is to be conducted outside Massachusetts, the CUHS will consult with the Office of General Counsel when any issue arises

regarding the applicable law of the jurisdiction for establishing who are “children” and “guardians”, see 45 CFR §46.402 (a), (e).

10.1.3 Allowable Categories

Research on children must be reviewed and categorized by the CUHS into one of the following groups:

1. Research not involving physical or emotional risk greater than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (i.e., **minimal risk**). [45 CFR 46.404]
 - The CUHS must find that adequate provisions are made for the permission of their parents or guardians, as set forth in 45 CFR §46.408.
 - The CUHS must find that adequate provisions are made for soliciting the assent of the children, as set forth in 45 CFR §46.408.
 - The permission of both parents is required if both parents are alive, known, competent, reasonably available, and have legal responsibility for the care and custody of the child. Otherwise the permission of one parent is required.
 - The CUHS may determine that the permission of one parent is sufficient, even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.
2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subject. [45 CFR 46.405]
 - The risk is justified by the anticipated benefit to the subjects;
 - The CUHS must find that adequate provisions are made for the permission of their parents or guardians, as set forth in 45 CFR §46.408
 - The CUHS must find that adequate provisions are made for soliciting the assent of the children, as set forth in 45 CFR §46.408.
 - The permission of both parents is required if both parents are alive, known, competent, reasonably available, and have legal responsibility for the care and custody of the child. Otherwise the permission of one parent is required.
 - The CUHS may determine that the permission of one parent is sufficient, even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.

3. Research involving greater than minimal risk and no reasonable prospect of direct benefit to the individual subject, but likely to yield generalizable knowledge about the subject's disorder or condition. [45 CFR 46.406]
 - The risk represents a minor increase over minimal risk;
 - The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
 - The CUHS must find that adequate provisions are made for the permission of their parents or guardians, as set forth in 45 CFR §46.408.
 - The CUHS must find that adequate provisions are made for soliciting the assent of the children, as set forth in 45 CFR §46.408.
 - The permission of both parents is required if both parents are alive, known, competent, reasonably available, and have legal responsibility for the care and custody of the child. Otherwise the permission of one parent is required.
4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children. [45 CFR 46.407]
 - Research in this category must be approved by the Secretary of the Department of Health and Human Services, and requires consent of both parents, or legal guardian (unless one parent is deceased, unknown, incompetent, or not reasonably available, or only one parent has legal responsibility for the care and custody of the child).
 - The CUHS must find that adequate provisions are made for the permission of their parents or guardians, as set forth in 45 CFR §46.408.
 - The CUHS must find that adequate provisions are made for soliciting the assent of the children, as set forth in 45 CFR §46.408.
 - The permission of both parents is required if both parents are alive, known, competent, reasonably available, and have legal responsibility for the care and custody of the child. Otherwise the permission of one parent is required

10.1.4 Parental Permission and Assent

10.1.4.1 Parental Permission

In accordance with 45 CFR 46.408(b) the CUHS 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 as stated in 45 CFR 46.116(a)(1-8) and any additional elements the CUHS deems necessary.

The CUHS may find that the permission of one parent is sufficient for research to be conducted under 45 CFR 46.404 or 45 CFR 46.405. Determination of whether consent must be obtained from one or both parents will be documented in the consent checklist when a protocol receives expedited review, and in meeting minutes when reviewed by the convened committee.

Consent from both parents is required for research to be conducted under 45 CFR 46.404, 45CFR 46.405, 45 CFR 46.406 and 45 CFR 46.407 unless:

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

The CUHS may waive the requirement for obtaining consent from a parent or legal guardian if:

- The research meets the provisions for waiver in 45 CFR 46.116(d)(1-4) and if the CUHS determines that the research protocol is designed for conditions or a subject population for which parental or guardian permission is not a reasonable requirements to protect the subjects (for example, neglected or abused children).
- An appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and that the waiver is not inconsistent with Federal State, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

Permission from parents or legal guardians must be documented in accordance with and to the extent required by 45 CFR 46.117.

10.1.4.2 Assent from Children

Because “assent” means a child’s affirmative agreement to participate in research, (45 CFR 46.402(b)), 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. When judging whether children are capable of assent, the CUHS must take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the CUHS deems appropriate.

When reviewing the proposed assent procedure and the form and content of the information conveyed to the prospective subjects, the CUHS again takes into account the ages, maturity, and psychological state of the children involved as well as the nature of the proposed research activity. For research activities involving adolescents whose capacity to understand approaches 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 will happen, 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 participation in research would involve.

If the CUHS 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 (e.g., new therapy when no other option is available), then the assent of the children is not a necessary condition for proceeding with the research. In addition, even where the CUHS determines that the minor subjects are capable of assenting, it still may waive the assent requirement in accord with 45 CFR § 46.116.

For children ages 7 and under, the CUHS recommends that the researchers verbally explain the study to the child, including its purpose, procedures, and potential risks and benefits (if appropriate, depending on the child's age, maturity and development). Generally, oral assent through the use of a script should be obtained from children ages 7 through 11 years of age. The CUHS may require written assent from older children. For children ages 11 and under in particular, investigators should consider obtaining assent in the presence of a parent or legal guardian, unless the study procedures are taking place in a setting (such as a school) where parents are not usually present.

Massachusetts regulations forbid the use of children in research involving controlled substances where the child has refused to consent to the research. 105 CMR §700.009(E) (4).

The Assent Form

When written assent is recommended, researchers should try to draft a 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 that it's up to the child to participate and that it's okay to say no;
4. explain whether 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.

For younger children, the document should be limited to one page if possible. Illustrations may be helpful, and larger type makes a form easier for young children to read. Studies involving older children or adolescents should include more information and may use more complex language.

10.1.4.3 Children Who are Wards

Under 45 CFR § 46.409(a), children who are wards of the state or any other agency, institution, or entity can be included in research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition, **only if such research is:**

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 subjects are not wards.

Even if the research meets the condition(s) above, 45 CFR § 46.409(b) requires that 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 CUHS) with the research, the investigator(s), or the guardian organization.

Massachusetts law (M.G.L. Chapter 119, et. seq.) allows the Department of Social Services ("DSS") to remove children from their parents' custody in certain circumstances, but the placement of a child in foster care does not automatically terminate all parental rights. Because these situations are complicated,

investigators who wish to use foster children as subjects in their research are urged to consult in advance with the CUHS.

10.2 Research Involving Pregnant Women, Human Fetuses and Neonates

10.2.1 Definitions

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

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

Fetus - the product of conception from implantation until delivery.

Neonate - a newborn.

Nonviable neonate - a neonate after delivery that, although living, is not viable.

Pregnancy encompasses the period of time from implantation until delivery. A woman is 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.

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

10.2.2 Research Involving Pregnant Women or Fetuses

Under 45 CFR § 46.204, 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, her consent 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 who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent;
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.

Experimentation on human fetuses is also regulated under Massachusetts law, M.G.L. Chapter 112C, § 12J(a), which states in part:

- I. No person shall use any live human fetus whether before or after expulsion from its mother's womb, for scientific, laboratory, research or other kind of experimentation. This section shall not prohibit procedures incident to the study of a human fetus while it is in its mother's womb, provided that in the best medical judgment of the physician, made at the time of the study, said procedures do not substantially jeopardize the life or health of the fetus, and provided said fetus is not the subject of a planned abortion. . . . This section shall not prohibit or regulate diagnostic or remedial procedures the purpose of which is to determine the life or health of the fetus involved or to preserve the life or health of the fetus involved or the mother involved. . . .
- II. No experimentation may knowingly be performed upon a dead fetus unless the consent of the mother has first been obtained, provided, however, that such consent shall not be required in the case of a routine pathological study. . . .

- III. No person shall perform or offer to perform an abortion where part or all of the consideration for said performance is that the fetal remains may be used for experimentation or other kind of research or study.
- IV. No person shall knowingly sell, transfer, distribute or give away any fetus for a use which is in violation of the provisions of this section. . . .

The Massachusetts statute includes criminal penalties, but states that those who have performed a procedure that allegedly violates the statute's provisions will not be held liable if: (i) the procedure received the written approval of a duly appointed IRB; and (ii) at the time the procedure was performed, there was not an outstanding court judgment that the procedure violated the statute. The IRB's written approval must state specifically that the procedure does not violate the provisions of the statute and must set forth a reasonable basis for this conclusion. M.G.L. Chapter 112C, § 12J(a)(V-VII). IRB members are themselves immune from liability under the statute if they acted in good faith in concluding that the procedure was lawful. M.G.L. Chapter 112C, § 12J(a)(VI).

10.2.3 Research involving neonates

[45 CFR 46.205]

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 of 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 covered by this subpart unless the following additional conditions have been met:

The CUHS 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 covered by this subpart 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.
6. 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.

Viable Neonates. A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of CUHS Review Process for Research Involving Children [see section 10.1].

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

[45 CFR 46.206]

1. Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, must be conducted only in accord with any applicable Federal, State, or local laws and regulations regarding such activities.
2. 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 subjects and all pertinent sections of this manual are applicable.

10.2.5 Research Not Otherwise Approvable

[45 CFR 46.207]

The Secretary of the Department of Health and Human Services (DHHS) will fund research that the CUHS does not believe meets the requirements of **Research Involving Pregnant Women or Fetuses** or **Research Involving Neonates** only if:

1. The CUHS 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
2. The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the Federal Register, has determined either:
 - a. That the research in fact satisfies the conditions of **Research Involving Pregnant Women or Fetuses**, as applicable; or
 - b. The following:
 - 1) 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;
 - 2) The research will be conducted in accord with sound ethical principles; and
 - 3) Informed consent will be obtained in accord with the provisions for informed consent and other applicable sections of this manual.

10.3 Research Involving Prisoners

Research involving prisoners is governed by 45 CFR 46, Subpart C, as applicable.

10.3.1 Applicability

This policy applies to all research conducted under the auspices of the University-Area institutions involving prisoners as subjects. Even though the CUHS may approve a research protocol involving prisoners as subjects according to this policy, investigators are still subject to the Administrative

Regulations of the Massachusetts Department of Corrections and any other applicable state or local law. [45 CFR 46.301]

10.3.2 Purpose

The incarceration of prisoners may affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research. In consequence, additional safeguards are appropriate for the protection of prisoners involved in research activities. [see 45 CFR 46.302]

10.3.3 Definitions

[45 CFR 46.303]

Prisoner – 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 which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing. The CUHS interprets this definition to include individuals who are sent by court order to alcohol/drug rehabilitation facilities.

These additional protections apply not just to individuals who are prisoners at the time they are enrolled in a study, but also to *those who become incarcerated during the course of a study*.

Minimal Risk – the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

10.3.4 Composition of the CUHS

[45 CFR 46.304]

In addition to satisfying the general requirements detailed in the CUHS section of this manual, when reviewing research involving prisoners, the CUHS must also meet the following requirements:

1. A majority of the CUHS (exclusive of prisoner members) must have no association with the prison(s) involved, apart from their membership on the CUHS.
2. At least one member of the CUHS must be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one IRB, only one IRB need satisfy this requirement.

10.3.5 Additional Duties of the CUHS

[45 CFR 46.305]

In addition to all other responsibilities prescribed for the CUHS in the CUHS Institutional Review Board and CUHS Review Process sections of this manual, the CUHS will review research involving prisoners and approve such research only if it finds that:

1. the research falls into one of the following **permitted categories** [45 CFR 46.306]:
 - a. study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
 - b. study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
 - c. research on conditions particularly affecting prisoners as a class (for example, research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that any study conducted or supported by DHHS may proceed only after certification to the Secretary, 45 CFR 46.305(c), and the Secretary of DHHS has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of the Secretary's intent to approve such research; or
 - d. research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, any study conducted or supported by DHHS may proceed only after certification to the Secretary, 45 CFR 46.305(c), and the Secretary of DHHS has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of the Secretary's intent to approve such research.
2. any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;

3. the risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers;
4. procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the CUHS justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;
5. the information is presented in language which is understandable to the subject population;
6. adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and
7. where the CUHS finds there may be a need for follow-up examination or care of subjects after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing subjects of this fact.

For research conducted or supported by DHHS, the institution responsible for the conduct of the research shall certify to the Secretary that the CUHS has fulfilled its duties under 45 CFR 46 Subpart C; the Secretary of the DHHS may assign further duties to the CUHS. 45 CFR §§ 46.305(b)-(c).

10.3.6 Waiver for Epidemiology Research

The Secretary of DHHS has waived the applicability of 45 CFR 46.305(a)(I) and 46.306(a)(2) for certain research conducted or supported by DHHS that involves epidemiologic studies and that meet the following criteria:

- (1) In which the sole purposes are
 - (i) To describe the prevalence or incidence of a disease by identifying all cases, or
 - (ii) To study potential risk factor associations for a disease, and
- 2) Where the IRB has approved the research and fulfilled its duties under 45 CFR 46.305(a)(2)–(7) and determined and documented that
 - (i) The research presents no more than minimal risk and no more than inconvenience to the prisoner-subjects, and
 - (ii) Prisoners are not a particular focus of the research.

The specific type of epidemiological research subject to the waiver involves no more than minimal risk and no more than inconvenience to the human subject

participants. The waiver would allow the conduct of minimal risk research that does not now fall within the categories set out in 45 CFR 46.306(a)(2).

The range of studies to which the waiver would apply includes epidemiological research related to chronic diseases, injuries, and environmental health. This type of research uses epidemiologic methods (such as interviews and collection of biologic specimens) that generally entail no more than minimal risk to the subjects.

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

10.3.7 Expedited Review and Exempt Research

Ordinarily, the CUHS will not expedite its review of research involving prisoners, although expedited review procedures are permitted under 45 CFR § 46.110 and 21 CFR § 56.110 for minor changes in approved research and for certain kinds of research involving no more than minimal risk. As noted above, with respect to research involving prisoners, the CUHS applies the definition of “minimal risk” set forth in 45 CFR § 46.303(d).

The exemptions set forth in 45 CFR § 46.101(b) do not apply to research involving prisoners. 45 CFR § 46.101(i), FN1.

10.4 Persons with Mental Disabilities or Persons with Impaired Decision-Making Capacity

Ordinarily, an investigator must obtain informed consent directly from prospective research subjects. When the prospective research subject is an adult whose own consent would not be legally effective because s/he lacks the capacity to give or communicate comprehending, informed consent, then research may be conducted only with the consent of the potential subject’s legally authorized representative (the “LAR”), which is also known as “surrogate consent.” This policy is designed to protect human subjects from exploitation and harm and, at the same time, make it possible to conduct research on problems that are unique to persons who are incompetent, or who have an impaired decision-making capacity.

The federal regulations define “*legally authorized representative*” as “an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject’s participation in the procedure(s) involved in the research.”⁵ Under Massachusetts law, this means the consent must come either from the legal guardian of the subject, or, in the case of research that is part of medical treatment, from the subject’s health care agent

⁵ 45 CFR 46.102(c)

(either as appointed under the Massachusetts health care proxy law, or as designated by a health care provider under the common law for obtaining consent to the provision of medical care and associated procedures). If the subject is able to give assent (affirmative agreement) as well, this is required but the CUHS may waive the requirement to seek assent if the subject is not competent to give it.

The Massachusetts Department of Mental Retardation regulations concerning research are useful in understanding how Massachusetts defines “guardian.” Those regulations state that “with respect to persons 18 years of age and older,” a guardian is the “individual, organization or agency, if any, that has been appointed legal guardian of the person found to be incompetent by a court of competent jurisdiction.”⁶ 115 CMR 10.02. Massachusetts law allows for guardianships to be created for persons who are judged to be mentally ill or mentally retarded, or for persons judged unable to communicate informed decisions. M.G.L. c. 201 §§ 6, 6A, 6B. The guardianship law does not enumerate all of the guardian’s authority, except to say that the guardian “shall have the care and custody of his ward . . . and the management of all his estate.” As this authority is generally accepted to mean that the guardian may take all actions for the ward that the ward might have taken if competent, there is no reason to believe that the ability to consent to research is not within the guardian’s authority. Indeed, this view is consistent with the manner in which the Department of Mental Retardation conducts its research using consent from guardians. See 115 CMR 10.00.

Massachusetts law provides for proxy consent for medical decisions to be given on behalf of a patient who lacks the capacity to consent. The law allows a competent adult to appoint a designated person as his or her “health care agent.”⁷ If the person then becomes incapacitated, and is in need of medical care, the health care proxy becomes empowered to make medical decisions on his or her behalf. If no health care agent has been appointed in advance, then medical care providers are authorized by the law to accept consent from “responsible parties,” under common law principles, usually meaning the patient’s next-of-kin.⁸ It is generally accepted in Massachusetts that if research involves the provision of medical care, a health care agent, whether appointed or holding that status by virtue of being a “responsible party,” may consent to that treatment and to the accompanying research.

In light of Massachusetts law, federal policy, and existing judicial opinions on the interrelationships of the two, it is unclear whether an IRB may approve a study that involves consent by an LAR for a cognitively-impaired adult to participate in non-medical research in the Commonwealth with more than minimal risk. In

⁶ 115 CMR 10.02

⁷ M.G.L. c. 201D

⁸ M.G.L. c. 201D, §16

such situations, before approving consent by an LAR, the CUHS must attend closely to the ethical considerations discussed in the Belmont Report (respect for persons (autonomy of subjects), beneficence, and justice) as well as the possible interpretations of existing law. The CUHS reasonably may look for guidance to closely similar situations in which the Belmont Report principles were applied, in determining appropriate consent/permission/assent processes for research under its review. A reasonable solution that balances interests frequently is possible following appropriate discussion and consideration by the CUHS. The Office of General Counsel will be consulted for each study involving adults unable to consent in Massachusetts for a determination of which individuals are legally authorized representatives under Massachusetts law to consent on behalf of subjects to their participation in the procedures involved in the research. For studies that involve adults unable to consent that will be conducted outside Massachusetts, the Office of General Counsel will be consulted regarding the applicable law of the jurisdiction for establishing who is an LAR, see 45 CFR § 46.102(c). However, it is possible that a study may be approved by the CUHS, but may not be permitted to proceed by the University (under advice of counsel or otherwise).

The CUHS may require investigators to conduct a preliminary **competency assessment** whenever there is a possibility of either impaired mental status or decision-making capacity in prospective subjects.

If feasible, the investigator must explain the proposed research to the prospective research subject even when a surrogate gives consent. Under no circumstances may a subject be forced or coerced to participate in a research study.

Under 104 C.M.R. § 31.00, et. seq., the Massachusetts Department of Mental Health has the jurisdiction to review and approve any human research “related to” the Department, its facilities or programs in which its “clients” are proposed subjects. Researchers whose proposals fall within the DMH’s jurisdiction must submit them to a DMH IRB for approval. In such cases, the CUHS ordinarily will designate the DMH IRB as the IRB of record and will enter into an IRB authorization agreement with DMH. However, in all such situations the CUHS independently will consider the study population, paying particular attention to the potential subjects’ ability to provide informed consent.

10.4.1 CUHS composition

The CUHS membership must include at least one member who has appropriate background and experience concerning individuals with mental disabilities or impaired decision-making capacity. Consideration may be given to adding another member who is a member of the population, a family member of such a person or a representative of an advocacy group for that population, or to consulting with such a person as appropriate.

10.4.2 Approval Criteria

Research involving persons with impaired decision-making capability may only be approved when the following conditions apply:

1. The investigator demonstrates to the CUHS that there is a compelling reason to include incompetent individuals or persons with impaired decision-making capacity as subjects. Incompetent persons or persons with impaired decision-making capacity must not be subjects in research simply because they are readily available.
2. The proposed research entails no significant risks, tangible or intangible, or if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the subject. Incompetent people or persons with impaired decision-making capacity are not to be subjects of research that imposes a risk of injury, unless that research is intended to benefit that subject and the probability of benefit is greater than the probability of harm.
3. Procedures have been devised to ensure that participant's representatives are well informed regarding their roles and obligations to protect incompetent subjects or persons with impaired decision making capacity. Health care agents [appointed under the Massachusetts health care proxy law] or guardians must be given descriptions of both the proposed research study and the obligations of the person's representative(s). They must be told that their obligation is to try to determine what the subject would do if competent, or if the subject's wishes cannot be determined, what they think is in the incompetent person's best interest.

10.4.3 Additional Concerns

Both investigators and CUHS members must be aware that some subjects' decision-making capacity may fluctuate. For subjects with fluctuating decision making capacity or those with decreasing capacity to give consent, a re-consenting process with surrogate consent may be necessary. **It is the responsibility of investigators to monitor the decision-making capacity of subjects enrolled in research studies and to determine if it is appropriate to request that a surrogate reaffirm consent after consideration of all consent issues.**

10.5 Subjects with Economic or Educational Disadvantages

Investigators at times perform research, both in the United States and abroad, with people who have limited resources in terms of finances, goods, and/or access to health care and other services. The CUHS pays particular attention to remuneration and other inducements that might encourage people with limited resources to participate in research projects in which they might not otherwise participate. Compensation should not be the sole grounds for participation in a

research project, and should not cause participants to assume risks that they would not ordinarily find acceptable.

The CUHS considers persons with limited resources to be vulnerable to the extent that inducements to participate in research may result in their acting against their own best interests. Where the population from which subjects will be recruited primarily consists of people with limited resources, the CUHS will look carefully at recruitment procedures, the potential risks in relation to the compensation being offered, and the potential benefits irrespective of compensation. The investigator will be asked to justify the compensation being offered. If the CUHS finds it to be coercive, then the CUHS will ask the investigator to provide alternative compensation so as not to impede the subjects' decision about whether they should participate in the research project.

11 Complaints, Non-compliance, and Suspension or Termination of CUHS Approval of Research

11.1 Complaints

The CUHS Chair and/or Executive Officer will promptly handle (or delegate staff to handle), and, if necessary, investigate all complaints, concerns, and appeals received by the CUHS from investigators, research participants and others.

The CUHS Chair or Executive Officer will designate an experienced office staff member to serve as the contact to receive communications from subjects or others, and to respond or, in the case of complaints or concerns, to forward them to the CUHS Chair and/or Executive Officer.

11.2 Non-compliance

All members of the University community involved in human subject research are expected to comply with the highest standards of ethical and professional conduct in accordance with applicable federal and state regulations and University, School, and CUHS policies governing the conduct of research involving human subjects.

11.2.1 Definitions

“Non-compliance” is defined as failure to comply with any of the regulations and policies described in this document and/or failure to follow the determinations of the CUHS. Non-compliance may be minor or sporadic, or serious and/or continuing.

“Minor or sporadic non-compliance” is noncompliance that is neither serious nor continuing.

“Serious non-compliance” occurs when the failure to follow any of the regulations and policies described in this document or a failure to follow the determinations

of the CUHS significantly: increases risk of harm to participants; decreases potential benefits; or compromises the integrity of the human research protection program.

“Continuing non-compliance” is a pattern of non-compliance that suggests a likelihood that instances of non-compliance will continue unless the CUHS intervenes. Continuing non-compliance also includes the failure to respond to a request to resolve an episode of non-compliance.

“Allegation of non-compliance” is an unproved assertion of non-compliance.

11.2.2 Review of Allegations of Non-compliance⁹

Whenever allegations of non-compliance or facts suggesting the likelihood of non-compliance are brought to the attention of the CUHS office, they will be reviewed by the CUHS Chair and/or Executive Officer, who may designate a subcommittee of one or more members to assist in fact gathering. The following documents will be reviewed, as available and appropriate:

1. All documents that pertain to the purported non-compliance;
2. The last approval letter from the CUHS;
3. The last approved CUHS application and protocol;
4. The last approved consent document;
5. The last approved Investigator’s Brochure;
6. The sponsored agreement(s) supporting the research; and
7. Any other pertinent information (e.g., questionnaires, DSMB reports, etc.).

Additional information or an audit of the research in question may also be requested. Where appropriate, the Dean’s office and/or the Office of the General Counsel may also be consulted.

The CUHS Chair and/or Executive Officer review each allegation of non-compliance and make a determination as to whether the allegation of non-compliance has a basis in fact. The CUHS Chair and/or Executive Officer may follow the Inquiry Procedures described below, if needed to make a determination. If the CUHS Chair and/or Executive Officer determine that the allegation of non-compliance has no basis in fact, no further action is taken under this policy. If the CUHS Chair and/or Executive Officer determine that the non-compliance has a basis in fact, it will be handled under Section 11.2.3, Review of Findings of Non-compliance.

If in the judgment of the CUHS Chair or Executive Officer, any allegations or findings of non-compliance warrant halting the research before completion of any review or investigation the CUHS Chair or Executive Officer may halt the

⁹ If in the judgment of the CUHS Chair and Executive Officer (with advice from the Office of the General Counsel as appropriate) the allegations also may involve research misconduct, the appropriate school authorities will be consulted to determine how the allegation shall be reviewed to ensure compliance with school and University policy, as well as any sponsor or other regulatory requirements.

research pursuant to Section 11.3, Suspension or Termination, with subsequent review by the CUHS.

11.2.3 Review of Findings of Non-compliance

The CUHS Chair and/or Executive Officer review each finding of non-compliance and make a determination as to whether the non-compliance is either serious or continuing. The CUHS Chair and/or Executive Officer may follow the Inquiry Procedures described below, if needed to make a determination. If the CUHS Chair and/or Executive Officer determine that noncompliance is neither serious nor continuing, and the investigator has agreed to a corrective action plan that they deem adequate, no further action is required and the CUHS is informed at the next convened meeting. Otherwise, the Inquiry Procedures described below will be followed and the matter will be presented to the CUHS at a convened meeting.

11.2.4 Inquiry Procedures

A determination may be made by the CUHS that an inquiry is necessary based on factors including but not limited to:

1. Complaint(s) that subjects' rights may have been violated;
2. Report(s) that investigator has made material changes to the approved protocol that may implicate subject welfare;
3. Unusual and/or unexplained harm to subjects in a study;
4. A federal (OHRP or FDA) investigation or audit of an investigator;
5. Repeated failure of investigator to report required information to the CUHS.

The CUHS Chair appoints a subcommittee consisting of CUHS members, and non-members if appropriate, to ensure fairness and expertise. The subcommittee is given a charge by the CUHS, which may include any or all of the following:

1. Review of protocol(s) in question;
2. Review federal investigation or audit of the investigator, if applicable;
3. Review of any relevant documentation, such as research files, correspondence, consent documents, case report forms, subject's investigational and/or medical files etc., as they relate to the investigator's execution of human subjects research;
4. Interview of appropriate personnel;
5. Preparation of a written report of the findings, which is presented to the full CUHS;
6. Recommendation of actions by the CUHS if appropriate.

The written findings of the subcommittee shall be provided to the investigator so that the investigator has the opportunity to submit a written response and can

request to appear at the CUHS meeting when the subcommittee report is reviewed.

11.2.5 Final Review

The results of the inquiry will be reviewed at a convened CUHS meeting where all members of the CUHS will receive a report from the subcommittee, any response offered by the investigator, a copy of the protocol, the initial application form updated with any changes, and the current consent document. The CUHS will first vote to determine whether the non-compliance is serious or continuing. If the CUHS determines that the non-compliance is neither serious nor continuing, the matter will be referred to the CUHS Chair and Executive Officer to determine a management plan. If the CUHS determines that the results of the inquiry substantiate a finding of serious or continuing non-compliance, it will consider the following actions, and other actions as appropriate:

1. Requiring a corrective action plan from the investigator;
2. Verifying that participant selection is appropriate and monitoring of the actual informed consent;
3. Increasing data and safety monitoring of the research activity;
4. Requiring a directed audit of targeted areas of concern;
5. Requiring a status report after each participant receives intervention;
6. Modifying the continuing review cycle;
7. Requiring additional Investigator and staff education;
8. Notifying current subjects, if the information about the non-compliance might affect their willingness to continue participation;
9. Modifying the protocol;
10. Modifying the information disclosed during the consent process;
11. Providing additional information to past subjects;
12. Requiring current subjects to re-consent to participation;
13. Suspending the study (See below);
14. Terminating the study (See below);
15. Suspending current research involving human subjects for which the investigator is responsible;
16. Terminating current research involving human subjects for which the investigator is responsible;
17. Prohibiting the investigator from conducting or supervising research involving human subjects for a period of time determined by the CUHS.

The investigator is informed in writing of the CUHS determination and the basis for the determination. If the CUHS determines that the non-compliance was serious or continuing, the results of the final review will be reported as described below in Section 12.

11.2.6 Additional Actions

A finding of serious or continuing non-compliance may have other results, for example:

1. Sponsor actions. In making decisions about supporting or approving applications or proposals covered by this policy, the sponsor may take into account, in addition to all other eligibility requirements and program criteria, factors such as whether the applicant has been subject to a termination or suspension as described above, and whether the applicant or the person or persons who would direct or has/have directed the scientific and technical aspects of an activity has/have, in the judgment of the sponsor, materially failed to discharge responsibility for the protection of the rights and welfare of human subjects.
2. University investigations. The conduct of the investigator or other personnel involved in a study involving human subjects may be the subject of a separate investigation or inquiry pursuant to University policies and procedures as carried out by appropriate University administrative bodies. Such an investigation or inquiry may result in disciplinary consequences up to and including dismissal.

11.3 Suspension or Termination

The CUHS has the authority to suspend or terminate approval of research that is not being conducted in accordance with the CUHS's requirements or that has been associated with unexpected serious harm to subjects. When the CUHS suspends or terminates its approval it will include a statement of its reasons in writing and report the suspension or termination promptly to the investigator and as described in Sections 11.4 and 12.

- **Suspension of Committee approval:** temporarily or permanently withdrawing approval for some or all research procedures short of permanently stopping all research procedures. Suspended research must undergo continuing review.
- **Termination of Committee approval:** permanently withdrawing approval for all research procedures. Terminated research is closed and does not require continuing review.

When study approval is suspended or terminated by the CUHS or other person authorized to suspend Committee approval, in addition to stopping all research activities, the CUHS will, as appropriate, inform any subjects currently participating that the study has been terminated. The CUHS will consider whether procedures for withdrawal of enrolled subjects are necessary to protect their rights and welfare. Such procedures might include: (1) Transfer to another investigator, (2) Transfer to standard clinical care, (3) Continuing in the research under the current investigator. If follow-up of subjects for safety reasons is permitted/required by the CUHS, the CUHS will require that the subjects should be so informed and that any adverse events/outcomes be reported to the CUHS and the sponsor.

Suspending or terminating approval of research that is not being conducted in accordance with the CUHS's requirements or that has been associated with

unexpected serious harm to subjects will be authorized by the convened committee. The CUHS Chair or Executive Officer are authorized to issue orders immediately suspending Committee approval, in which case the decision will be reported to the convened committee for review.

11.4 Reporting

Serious or continuing noncompliance with regulations or with CUHS requirements or determinations, and suspensions or terminations of CUHS approval, will be reported to the appropriate regulatory agencies and institutional officials according to the procedures in Section 12.

12 Reporting to Regulatory Agencies and Institutional Officials

CUHS staff will initiate the following procedures as soon as the CUHS:

- a) Determines that an event may be considered an unanticipated problem involving risks to subjects or others;
 - b) Determines that non-compliance was serious or continuing; or
 - c) Suspends or terminates approval of research.
- 1) The Executive Officer or designee prepares a letter that contains 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 approval of research)
 - b) Name of the institution conducting the research
 - c) Title of the research project(s) and/or grant proposal(s) in which the problem occurred
 - d) Name of the principal investigator on the protocol(s)
 - e) Number of the research project assigned by the CUHS and the number of any applicable federal award(s) (grant, contract, or cooperative agreement)
 - f) A detailed description of the problem(s) including the CUHS's findings, whether preliminary or final, and the reasons for its decision (if applicable)
 - g) Actions the institution is taking or plans to take to address the problem (e.g., revise the protocol, suspend subject enrollment, terminate the research, revise the informed consent document, inform enrolled subjects, increase monitoring of subjects, etc.)
 - h) Plans, if any, to send a follow-up or final report by the earlier of

- (1) A specific date; or
 - (2) When an investigation has been completed or a corrective action plan has been implemented
- 2) The Executive Officer or designee sends the letter to some or all of the following persons or entities, after consultation with the CUHS Chair:
- a) The CUHS (by including the letter in the next agenda packet as an information item)
 - b) The Institutional Official
 - c) The following agencies:¹⁰
 - i) OHRP, if the study is subject to DHHS regulations or subject to a DHHS federalwide assurance.
 - ii) FDA, if the study is subject to FDA regulations.
 - iii) If the study is conducted or funded by any Federal Agency other than DHHS that is subject to The Common Rule, the report is sent to OHRP or the head of the agency as required by the agency.
 - d) Principal investigator
 - e) Sponsor, if the study is sponsored
 - f) Contract research organization, if the study is overseen by a contract research organization
 - g) Department chair and/or supervisor of the investigator
 - h) The Privacy Officer of a covered entity (as defined by HIPAA), if the event involved unauthorized use, loss, or disclosure of individually-identifiable patient information from that covered entity
 - i) The Information Security Officer of an organization if the event involved violations of information security requirements of that organization
 - j) Harvard's Division of Risk Management and Audit Services
 - k) Harvard's Office of the General Counsel
 - l) Others as deemed appropriate by the CUHS Chair

The Executive Officer ensures that all steps of this reporting policy are completed promptly, and in all cases within 30 days of the initiating action. For more serious actions, the Executive Officer will expedite reporting.

¹⁰ 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 mechanism.

13 Investigator Responsibilities

Investigators are ultimately responsible for the conduct of research. While Investigators may delegate research responsibility, they must maintain oversight and retain ultimate responsibility for research conducted under their auspices.

In order to satisfy the requirements of this policy, investigators who conduct research involving human subjects must:

- develop and conduct research that is in accordance with the ethical principles in the Belmont Report
- develop a research plan that is scientifically sound and minimizes risk to the subjects;
- have sufficient resources necessary to protect human subjects, including: supervision, a sufficient number of appropriately trained staff, and appropriate support services.
- protect the rights and welfare of prospective subjects;
- have plans to monitor the data collected for the safety of research subjects,
- have a procedure to receive complaints or requests for additional information from subjects and respond appropriately,
- ensure that pertinent laws, regulations, and institutional procedures and guidelines are observed by all participating faculty, students and research staff;
- ensure that all research involving human subjects receives CUHS review or appropriate determination of exemption before commencement of the research;
- comply with all CUHS decisions, conditions, and requirements;
- obtain and document informed consent as required by the CUHS;
- ensure that protocols receive timely continuing CUHS review and approval;
- report unexpected problems or serious harm to subjects to the CUHS;
- obtain CUHS review and approval in writing before changes are made to approved protocols or consent forms;
- seek CUHS assistance when in doubt about whether proposed research requires CUHS review.

13.1 Investigators

Principal Investigators

At the University-Area institutions **faculty members** may serve as Principal Investigator or as faculty sponsor on a research project involving human subjects if their School allows them to serve as Principal Investigator on applications for sponsored funding to be administered through the University.

Adjunct faculty of the University, including lecturers (unless School policy specifically allows them to serve as Principal Investigator), and any other investigator whose status is considered to be “in training” (e.g., students and postdoctoral fellows) may not serve as a Principal Investigator, but may serve as a co-investigator.

The CUHS ordinarily recognizes one Principal Investigator (PI) for each study. The PI has ultimate responsibility for the research activities.

Protocols that require skills beyond those held by the Principal Investigator must be modified to meet his or her skills, or the Principal Investigator must include on the protocol one or more additional qualified co-investigator(s).

Student Investigators

Students may not serve as Principal Investigators on research studies involving human subjects. They must have a faculty sponsor who fulfills the Principal Investigator eligibility criteria and who will serve as Principal Investigator and faculty advisor on the study.

Research Team

The Research Team is comprised of the PI and other individuals who contribute to the scientific development or execution of a project in a substantive, measurable way, whether or not they receive salaries or compensation under the protocol.

13.2 Protocol Development

When developing a protocol, the investigator or a member of the research team may contact the CUHS Office for a determination as to whether the proposed project constitutes human subjects research, and if so, what level of review is required. Contact with CUHS Office may be by phone, letter, or email and must include a brief description of the proposed research. The CUHS Office will respond to the investigator or member of the research team by phone, letter, or email.

Using the CUHS protocol application, the investigator must carefully develop a Description of Study (investigator/local research plan) and consent form(s), making sure that consent form information is in agreement with the research plan. See Section 7.4.3.

The investigator must submit the CUHS application and all attachments to appropriate institutional regulatory committee offices (e.g., Radiation Safety Committee, etc.) for review and approval.

If research is externally sponsored, the CUHS will receive a copy of the application for funding; if CUHS notes a significant variation between the DHHS application and the CUHS protocol, the investigator must identify and justify the discordance.

13.3 Changes to Approved Research

Investigators must seek CUHS approval before making changes in approved research during the period for which CUHS approval has been given, unless the change is necessary to eliminate an immediate hazard to the subject (in which case the CUHS must then be notified at once).

Minor changes (i.e., changes that do not involve increased risk or discomfort) may be authorized by the CUHS Chair or his/her designee. A letter specifying the changes requested and a revised consent form (if applicable) should be sent directly to CUHS Office. The CUHS Office must reply in writing to indicate approval.

Note: CUHS approved amendments to ongoing research do NOT extend the original approval expiration date.

13.4 Continuing Review after Protocol Approval

Ongoing research studies must be reviewed by the CUHS at least annually, or more often if the CUHS finds that the degree of risk to subjects warrants more frequent review. **This renewal must take place prior to the end of the approval period noted in the Report of Committee Action;** otherwise, subject participation, including recruitment and enrollment, must be suspended, unless doing so would pose a risk of harm to subjects.

It is the investigator's responsibility to submit a timely continuing review application. See Section 7.4.4 for a description of the information that must be included. As a courtesy, the CUHS Office will send Renewal Notices to the investigator at 75, 45, and 15 days prior to the expiration of each approved protocol. The investigator should allow sufficient time for development and review of renewal submissions. **Note:** The "approval date" and the "approval expiration date" are listed on all CUHS certifications.

The convened Committee must use the Reviewer Checklist to determine whether research meets the regulatory criteria for approval when undergoing continuing review.

Continuing review must occur as long as:

- Research remains active for long-term follow-up of subjects, even when the

research is permanently closed to the enrollment of new subjects and all subjects have completed all research-related interventions.

- The remaining research activities include collection or analysis of private identifiable information.

13.5 Required Reports to the CUHS

13.5.1 Unanticipated Problems

Prompt reporting to the CUHS Office is required for the problems described in Section 7.8.

13.5.2 Complaints, Non-compliance, and Protocol Deviations

Investigators must promptly report to the CUHS all non-compliance by research staff, protocol deviations, and complaints and concerns from subjects, except those manifestly lacking in substance.

13.5.3 Progress Reports

Investigators must report the progress of the research to the CUHS in the manner and frequency prescribed by the CUHS, but no less than once a year.

When an approved research project is completed, the investigator should promptly notify the CUHS via email or letter.

13.6 Investigator-Required Record Keeping

Investigators are responsible for retaining copies of all CUHS-approved documents for a minimum of three years following the completion of the study.

Where written informed consent is indicated, copies of all signed consent forms must be stored securely by the investigator for a minimum of three years following the completion of the research.

13.7 Conflict of Interest – Investigators

All investigators must follow the appropriate School and University Conflict of Interest Policies when conducting research funded by the National Science Foundation or the Public Health Service. Investigators must identify for resolution under those policies' specific procedures any potential conflict of interest associated with a study, including but not limited to their personal investment in or other financial relationship with a company that might profit from the study.

Regardless of the source of funding for the research, as part of the application process for CUHS approval, all investigators must disclose any potential or

actual financial conflict of interest they may have as a result of the sponsorship for that study, or as a result of rights in intellectual property based directly on results of the study.

If the investigator is permitted to proceed with the study following consultation and/or review concerning potential conflict of interest, the research consent form provided to subjects should include an appropriate description of any relationship that involves, or creates the appearance of, a conflict of interest.

If, during the course of an approved study, a conflict of interest arises for an investigator or any member of the research team with respect to the study, the individual is required to notify the CUHS Office promptly of the conflict. The CUHS Officers will review the conflict as a modification to the protocol.

13.8 Training / Continuing Education of Investigator and Research Team

As stated above, one component of a comprehensive human research protection program is an education program for all individuals involved with research subjects. Harvard University is committed to providing training and continuing education for investigators and members of their research team related to ethical concerns and regulatory and institutional requirements for the protection of human subjects.

Initial Education

Investigators must complete appropriate training in human research ethics before submitting their first application to the CUHS, or begin training and commit to completing it before the initiation of their study. CUHS may make approval of an application contingent upon receipt of proof of completion of the appropriate training.

Investigators who complete the online training course, Harvard Ethics Training in Human Research (HETHR), will automatically receive their certification; an investigator who elects to meet the initial education requirement by completing the CITI Course in the Protection of Human Subjects in Research (www.citiprogram.org) or similar training, must submit proof of completion to the CUHS. HETHR, CITI, or NIH training are required for NIH funded studies. CUHS will consider the sufficiency of other training, as disclosed in the application, Q. 3 (b), in light of the nature of the proposed study.

Faculty Sponsor Obligations, Human Subjects Research Ethics Training

Faculty sponsors who review and approve applications for students to submit to the CUHS must familiarize themselves with the STATEMENT OF POLICIES AND PROCEDURES GOVERNING THE USE OF HUMAN SUBJECTS IN RESEARCH AT HARVARD UNIVERSITY *as voted by the President and Fellows*

of Harvard College, September 22, 2003, Appendix A, and ensure also that the student applicant is familiar with it. Where the research poses greater than minimal risk, the faculty sponsor must have experience carrying out research with a comparable level of risk, and the student must complete HETHR online training.

Investigators who are also members of the CUHS or part of the CUHS administration will complete the training requirements for CUHS members and staff described in this policy under 5.6.

Additional Resources

1. Human research protection information will be made available on the CUHS Office website on an ongoing basis to ensure that the University research community is apprised of current regulatory and policy requirements and training opportunities.
2. Federal Office for Human Research Protections: links to guidance and other relevant information on the OHRP website will be maintained on the CUHS Office website.

13.9 Subject Recruitment

CUHS approval is required for all recruiting procedures and materials. Recruitment materials must be consistent with the approved CUHS protocol, accurate, and not coercive. Investigators are responsible for recruiting research subjects in a manner that is fair, ethical, and equitable.

13.10 Payment to Subjects

Payment to research subjects may be an incentive for participation or a way to reimburse a subject for travel and other 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 coercion of subjects. In general payments should be proportional to the degree of risk, inconvenience, or discomfort associated with participation.

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

The consent form must describe the terms of payment and the conditions under which subjects would receive partial payment or no payment (e.g., if they withdraw from the study before their participation is completed).

Where monies for **payment are administered through the University**, the University Tax Office may require certain identifying information to issue payments for participation in research studies and to issue IRS 1099 forms where appropriate; in such cases, the consent form must inform subjects that

they will be asked to provide that identifying information in order to be eligible for payment.

13.11 Investigator Concerns

Investigators who have concerns or suggestions regarding University-Area human research protection programs should convey them to the CUHS staff or chair, Institutional Official, or other appropriate school officials (e.g., school dean, departmental chair, center director). The Institutional Official will research any issue presented to him or her, and may convene the parties involved to respond to the investigator or to make procedural or policy modifications, as warranted.

14 Health Insurance Portability and Accountability Act (HIPAA)

14.1 Background

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) required Congress to enact a health information privacy law (the "Privacy Rule"), which it did in August 2002. The Privacy Rule, which became effective on April 14, 2003, is intended to protect the privacy of an individual's health care information. It creates a federal "floor" of protection, with the understanding that states may create additional rights and protections.

14.2 Effects of HIPAA on Research

HIPAA's definition of research is identical to that of the Common Rule: "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge." Under HIPAA, "covered entities" must manage what is called "protected health information," or "PHI," in accordance with the Privacy Rule. Harvard is a hybrid entity, meaning that only certain divisions (including the University Health Services and the Bureau of Study Counsel) must follow the HIPAA regulations. Thus, any research taking place at a "covered entity" within the University, and involving PHI, must comply with the Privacy Rule.

14.3 HIPAA Authorized Access to Protected Health Information

HIPAA provides for the following means of gaining access to PHI: authorizations; IRB waiver under the HIPAA criteria; limited data sets; and de-identification of data sets. It is the responsibility of the covered entity to ensure that it only releases PHI to an investigator under one of these HIPAA compliant means .

14.4 Patient Rights and Research

Under HIPAA, patients have the right to receive a Notice of Privacy Practices, the right to access, inspect, and receive a copy of one's own PHI, the right to request an amendment to one's own PHI, and the right to an accounting of certain

disclosures of PHI that occur outside the scope of treatment, payment, and health care operations that have not been authorized.

14.5 HIPAA and Existing Studies

Studies at a covered entity that enrolled human subjects prior to April 14, 2003 may proceed according to the protocol documents that were approved by the CUHS at that time; that is, researchers may continue to collect and use data gathered from these subjects, and no new documentation is required. However, any subject enrolled in a research project at a covered entity AFTER April 14, 2003 must sign a HIPAA-compliant authorization form unless the IRB waives consent under HIPAA criteria, or the research involves a limited data set of de-identified data. If the research involves a limited data set, then the researcher and the covered entity must have in place a HIPAA compliant data use agreement that addresses the use of the data and patient privacy concerns. If an authorization form is used, it would be in addition to the existing Informed Consent document. In a few cases, the Informed Consent document may be combined with a HIPAA authorization.

15 FDA Regulated Research

It is the policy of the CUHS to enter into Institutional Authorization Agreements with hospitals or other institutions that have appropriate federalwide assurances and IRBs with medical, scientific and local expertise to carry out the review of applications for research governed by FDA regulations. In certain cases, such as a study that combines investigational drug or device use with significant research elements that are not FDA regulated (psychological testing, for example) the CUHS may arrange for review by an IRB qualified to review FDA-regulated research, and continue to oversee the study as well.

16 Special Topics

16.1 Certificate of Confidentiality

16.1.1 Statutory Basis for Protection

Protection against compelled disclosure of identifying information about subjects of 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."

Certificates of Confidentiality constitute an important tool to protect the privacy of research study subjects. Certificates are issued by the National Institutes of Health (NIH) to protect identifiable research information from forced disclosure. They allow the investigator and others who have access to research records to refuse to disclose identifying information on research subjects in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level.

Certificates of Confidentiality may be granted for studies collecting information that if disclosed could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy to subjects.

Certificates may be granted even if the study is funded from non-federal sources, or has no external funding.

The Certificate goes beyond the consent form in ensuring confidentiality. Without the Certificate, researchers can be required by a court-ordered subpoena to turn over research documents (usually as part of a criminal investigation of the subjects or as part of a civil lawsuit where a subject is a party).

Any investigator planning or conducting research in which identifiable sensitive information is gathered from human subjects may apply for a Certificate of Confidentiality. Research can be considered "sensitive" if it involves the collection of:

- information about sexual attitudes, preferences, practices;
- information about personal use of alcohol, drugs, or other addictive products;
- information about illegal conduct;
- information that could damage an individual's financial standing, employability, or reputation within the community;
- information in a subject's medical record that could lead to social stigmatization or discrimination; or
- information about a subject's psychological well-being or mental health.

This list is not exhaustive. Researchers contemplating research on a topic that might qualify as sensitive should contact the CUHS Office for help in applying for a certificate.

The CUHS may require investigators to apply for a Certificate of Confidentiality as a condition of approval.

16.1.2 Limitations

The protection offered by a Certificate of Confidentiality is not absolute. A Certificate protects research subjects only from legally compelled disclosure of their identity. It does **not** restrict voluntary disclosures.

For example, a Certificate does not prevent researchers from making mandatory reports to appropriate authorities about matters such as child abuse, a subject's threatened violence to self or others, or from reporting certain communicable diseases. (However, the possibility of such disclosures should be clearly stated in the informed consent form that research subjects are asked to sign.)

In addition, 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 subject if

- the subject (or, if he or she is legally incompetent, his or her health care agent or legal guardian) consents, in writing, to the disclosure of such information;
- 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
- release of such information is required by the Federal Food, Drug, and Cosmetic Act or regulations implementing that Act.

16.2 Mandatory Reporting

While preparing a research protocol, investigators must keep in mind that the Commonwealth of Massachusetts mandates reporting by certain persons to designated officials and/or agencies, in cases of suspected child abuse and neglect; M.G.L. c. 119 sec. 51A; see Department of Social Services FAQ at <http://www.doe.mass.edu/acls/abecert/update/041897upd.html> .

Investigators should consult the CUHS Office to determine if potential subjects should be advised of mandatory reporting requirements during the informed consent process.

16.3 Harvard University Students and Employees as Subjects

When Harvard University students and/or employees are being recruited as potential subjects, researchers must guard against coercion of these subjects. To minimize the risk of coercion, investigators should avoid, whenever possible, the use of their own students and employees in research studies. Participation in a research study must never be a condition of employment, insurance, grades, promotion, or any other benefits or bonuses. Investigators should solicit subjects via public forums, such as bulletin board notices, flyers, advertisements in newspapers, and announcements in classes **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, thereby alleviating pressure to participate.

16.4 Psychology Department Study Pool

The Faculty of Arts and Sciences Psychology Department administers a Study Pool. Students in participating Psychology courses may either sign up to participate in up to five study hours for course credit or complete alternate assignments determined by their course instructor. Members of the community may also participate for cash compensation. Graduate students, undergraduate thesis writers, and faculty may apply to use this Study Pool for their research.

The Pool serves both to introduce students and members of the community to the process of psychological research and to provide members of the department with participants for their research studies. The Study Pool website is located at <http://studypool.wjh.harvard.edu/>.

The Study Pool is guided by two principles: 1) Participation must be educational and 2) participation must be voluntary.

The Department of Psychology conducts all Study Pool research and training in accordance with the ethical guidelines set forth by the American Psychological Association, as well as with CUHS policies and procedures. Any researcher using the Study Pool must have successfully completed the HETHR online training or equivalent as accepted by the CUHS. Department policies governing the use and operation of the Study Pool are regularly reviewed, and revisions pertaining to research activities are submitted to the CUHS for approval.

16.5 Student Research

All non-exempt research involving human subjects, including that conducted by students, is subject to review. Some student projects may not meet the regulatory definition of research since they are designed to instruct the students in research methods rather than being designed to develop or contribute to generalizable knowledge; the potential for risk to subjects who participate in

student research will determine whether the protocol and consent information must be reviewed by the CUHS or by the course instructor(s). CUHS may require that students complete training in the ethics of human subjects research as a condition of approval of their application.

The objective of the review, whether conducted by the CUHS or by the course instructor(s), is to ensure that the class assignment includes appropriate precautions for protecting human subjects—an important aspect of education in research methods.

The CUHS has developed the following procedures to facilitate review.

16.5.1 Course projects

A faculty member who wants students in his or her course to conduct research involving human subjects as a class assignment should complete a CUHS application describing the nature of the research to be conducted by the students. Although exact details of each project will not be available, the application should describe the overall nature of the work to be done, the characteristics of subjects, how they will be recruited, the range of activities they may be asked to participate in, possible risks and benefits, procedures for obtaining informed consent, confidentiality protections, and any other relevant information as requested on the CUHS application form.

If the proposed projects seem likely to involve no more than minimal risk to subjects, the course application will be reviewed by the CUHS Office and approval will be granted on the understanding that individual student projects will be reviewed, ordinarily using the CUHS application form, by the instructor or another experienced member of the course teaching staff, and any projects not falling within the boundaries of the approved course application will be referred to the CUHS to determine if further review is required. If the projects described in the course application seem likely to involve more than minimal risk, “blanket” approval will not be granted, and the students will be asked to submit individual applications to the CUHS.

For student projects approved under these procedures, the instructor assumes responsibility for the conduct of the student research and is responsible for ensuring that projects are conducted in accordance with the requirements of CUHS approval. Instructors should educate students on the ethical conduct of research and help them prepare the CUHS application form.

16.5.2 Independent Study, Theses, and Dissertations

These research activities are considered to meet the federal definition of human subjects research and must be independently submitted to the CUHS by the student-researcher. Since students are not eligible to serve as Principal Investigators, they must have a faculty sponsor who meets their school’s Principal Investigator eligibility criteria; *the faculty sponsor is ultimately*

responsible for the protection of the subjects, even if the student is the primary researcher and actually directs the project.

16.6 Genetic Studies

Genetic research studies may create special risks to human subjects and their relatives, including medical, psychological, social, and economic risks, such as the possible loss of privacy, insurability, and employability; change in immigration status and limits on education options; and possible creation of social stigma. Knowledge of one's genetic make-up may also affect one's knowledge of personal disease risk status, or that of family members.

In studies involving genetic testing, the following questions need to be addressed by completing an additional questionnaire, found at the CUHS website [\[link\]](#):

1. Will test results be given?
2. Will disease risk be quantified, including the limits on certainty of the testing?
3. Will a change in a family relationship be disclosed if discovered, such as mistaken paternity?
4. Does the subject or family member have the option not to know the results? How will this decision be recorded?
5. Could other clinically relevant information be uncovered by the study? How will disclosure of this added information occur?
6. Do any practical limitations exist on the subject's right to withdraw from the research, withdraw data, and/or withdraw samples given for the research?
7. Is the subject permitted to participate in the study while refusing to have genetic testing (such as in a treatment study with a genetic testing component)?

For DNA banking studies, several questions need to be addressed, including:

1. Will DNA be stored or shared? If shared, will the subject's identity be known by the new recipient investigator?
2. Will the subject be contacted in the future by the investigator to obtain updated clinical information?
3. How can the subject opt out of any distribution or subsequent use of his/her genetic material?

16.7 Research Involving Coded Private Information or Biological Specimens

Harvard University policy is based on the OHRP guidance document entitled, **“Guidance on Research Involving Coded Private Information or Biological**

Specimens” (August 10, 2004

<http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf>). This document:

- 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).
- Reaffirms OHRP policy that, under certain limited conditions, research involving **only** coded private information or specimens is not human subjects research.
- Provides guidance on who should determine whether human subjects are involved in research.

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.

Under the definition of human subject in Section 2 of this policy, *obtaining* identifiable private information or identifiable specimens for research purposes constitutes human subjects research. *Obtaining* means receiving or accessing identifiable private information or identifiable specimens for research purposes. This includes an investigator’s use, study, or analysis for research purposes of identifiable private information or identifiable specimens already in the possession of the investigator.

In general, 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 through coding systems. Private information or specimens are not considered to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Research involving **only** coded private information or specimens do **not** involve human subjects if the following conditions are both 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, for example:

- (a) the key to decipher the code is destroyed before the research begins;
- (b) the investigators and the holder of the key enter 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);
- (c) there are CUHS-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or
- (d) there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

In some cases an investigator who obtains coded private information or specimens about living individuals under one of the conditions cited in 2(a)-(d) above may (1) unexpectedly learn the identity of one or more living individuals, or (2) for previously unforeseen reasons now believe that it is important to identify the individual(s). If, as a result, the investigator knows, or may be able to readily ascertain, the identity of the individuals to whom the previously obtained private information or specimens pertain, then the research activity now would involve human subjects. Unless this human subjects research is determined to be exempt (See Section 7.2), CUHS review of the research would be required. Informed consent of the subjects also would be required unless the CUHS approved a waiver of informed consent (See Section 9.3).

Who Should Determine Whether Coded Private Information or Specimens Constitutes Human Subjects Research

The investigator in consultation with the CUHS Chair or Officer will determine if the research involving coded information or specimens requires CUHS review. If the request is oral (by phone or in person) or by email, it is the investigator's responsibility to maintain documentation of such a decision. If the request is submitted in writing, it must include sufficient documentation of the activity to enable a determination by the CUHS Officer. Written submissions will be responded to in writing and a copy of the submitted materials and determination letter/email will be kept on file.

16.8 Investigator Self-Experimentation

The University-Area schools do not prohibit investigator self-experimentation. However, as it would with any proposed research, the CUHS will review each protocol and determine the appropriateness of the research. The CUHS will consider as part of its review the level of self-experimentation and the potential risks and benefits to the investigator as research subject.

A main concern for the CUHS when reviewing a protocol that involves self-experimentation, is that the ideation of a novel concept may outweigh the investigator's concern for his/her own welfare. For this reason, the CUHS may require that a CUHS member obtain informed consent from the investigator. The CUHS also may institute additional safeguards for the research project, such as shorter review periods and monthly progress reports.

16.9 International Or Off-Site Research, And Other Projects That Require External Verification

For international research, the CUHS 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 NIH-registered) and/or local letters of support. The source of this information will depend on the nature of the study, on the country and on the resources available to the PI. At its discretion, the CUHS also may request that someone with special knowledge of the local research context either review a particular protocol, or attend an IRB meeting to provide the CUHS with recommendations based on his or her expertise.

In some circumstances where research may be performed internationally and/or in settings where there are no IRBs, the CUHS may, prior to approval of the research, 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 will be taking place, such as local IRBs or ethics committees, other Harvard researchers with knowledge of the region, or other experts on the region.

At its discretion, the CUHS may require verification from someone other than a researcher (for example, a Department Chair or CUHS member) that changes to documents or procedures, agreed upon by the researcher and the CUHS, have been made. Although uncommon, this external verification may be required by the CUHS if it has made more than one unsuccessful attempt to receive documentation of changes from the researcher, or if it has received a report from study personnel, study participants, or others, that changes it recommended were not implemented.