

addition to the above materials, any updated regulations, education and policy materials are provided to CHS staff. CHS staff are afforded opportunities to attend training sessions and conferences addressing human research protections offered through Harvard and/or outside organizations.

#### **4. Initial Review of Research**

Each Investigator whose proposed research is subject to the jurisdiction of the CHS must submit a CHS Application, which can be found on the CHS website: <http://www.hms.harvard.edu/orsp/human/human.html>. In addition to the application, all materials related to the research study must be submitted to the CHS office. These materials include:

- CVs/Biosketches for the Investigator and research personnel with human studies responsibilities (including members of the team who interact with participants or handle data/specimens containing participant identifiers);
- HETHR or equivalent human subjects protection certification (such as CITI or NIH) for all research personnel with human studies responsibilities (including members of the team who interact with participants or handle data/specimens containing participant identifiers);
- IRB approvals from appropriate institutions, or letter of support if the institution does not require IRB review, as applicable;
- All funding application/s (including grants, subcontracts and clinical trial agreements) supporting the research;
- The full protocol;
- The sponsor protocol (when one exists);
- The complete DHHS-approved protocol (when one exists);
- Recruitment materials (cover letters, fliers, brochures, email notices);
- Study materials (telephone scripts, question guides, written questionnaires and surveys);
- Educational materials (information sheets, study guides);
- Consent materials, including any requests for waivers;
- HIPAA materials (including any waiver requests and proposed authorizations);
- Investigator's Brochure (or package insert or pages from the *Physicians Desk Reference*, if a marketed drug).

##### **4.1. Office Procedures for Processing New Applications**

Applications received by the CHS office are date-stamped and screened for completeness (meaning that all questions on the application have been answered, including a "N/A" when a question is not applicable, and that appropriate signatures appear on the signature page); the relevant study information is entered into the HIRBERT database by CHS staff, and a study number and file is generated. The CHS Administrator will designate a CHS staff member to be responsible for the study, including pre-reviewing the materials and seeing the proposal through the approval process.

The CHS staff will communicate with the Investigator (or personnel designated by the Investigator) regarding any requests for changes or additional documentation needed for a thorough review by the CHS, or CHS Chair or members for expedited review (see Section 4.9). The CHS staff serve as the primary liaisons between the Investigator and the CHS and, by virtue of their knowledge of the study, can provide information to assist the CHS in the decision making process.

Incomplete submissions (lacking requisite forms, signatures, or documentation) will not be placed on the CHS monthly agenda. However, should an Investigator exercise his/her discretion not to make recommended changes as a result of the CHS staff pre-review, the research proposal will be placed on the agenda along with a memorandum regarding the issues of concern for the CHS' consideration.

## **4.2. Definitions**

The CHS uses the following definitions set forth in DHHS regulations 45 CFR § 46.102 and FDA regulations 21 CFR § 50.3 and 56.102:

- i. Research* as defined by DHHS regulations is a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.
- ii. Research subject to regulation*, and similar terms are intended to encompass those research activities for which a federal department or agency has specific responsibility for regulating as a research activity, such as IND requirements administered by the FDA. It does not include research activities which are incidentally regulated by a federal department or agency solely as part of the department's or agency's broader responsibility to regulate certain types of activities whether research or non-research in nature (for example, Wage and Hour requirements administered by the Department of Labor).
- iii. Human subject* as defined by DHHS regulations means a living individual about whom an Investigator (whether faculty, staff or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.
- iv. Research Involving Human Subjects*: means an activity that meets the DHHS definition of "research" and involves "human subjects" as defined by DHHS, or that meets the FDA definition of "research" and involves "human subjects" as defined by the FDA.
- v. Intervention* includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment

that are performed for research purposes. *Interaction* includes communication or interpersonal contact between investigator and subject.

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

For those studies involving clinical investigations, the CHS uses the FDA's definitions (set forth in 21 CFR § 56.102 (23)) as follows:

- viii. *Clinical investigation* or research defined FDA regulations means any experiment that involves a test article and one or more human subjects, and that either meets the requirements for prior submission to the FDA under section 505(i) or 520(g) of the Federal Food Drug and Cosmetic Act (i.e. 21 U.S.C. 355(i) or 360j(g)), or does not meet the requirements for prior submission to the FDA under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit. The term does not include experiments that meet the provisions of part 58 (i.e. 21 CFR Part 58, "Good Laboratory Practice for Nonclinical Laboratory Studies"), regarding nonclinical laboratory studies. The terms *research*, *clinical research*, *clinical study*, *study*, and *clinical investigation* are deemed to be synonymous. In addition:
- An experiment is subject to the requirements for prior submission to the FDA under section 505 (i) of the Food, Drug and Cosmetic Act when it involves any use of a drug other than the use of a marketed drug in the course of medical practice,
  - An experiment is subject to the requirements for prior submission to the FDA under section 520(g) of the Food, Drug and Cosmetic Act when it involves the evaluation of the safety or effectiveness of a medical device.
- ix. *Human subject* as defined by FDA regulations means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject is also an individual on whose specimens a medical device is used.
- x. *Test article* means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the Food and Drug Act or under sections 351 or 354-360F of the Public Health Service Act.

- xi. Investigator* means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject) or, where an investigation is conducted by a team, the responsible leader of that team.

#### **4.3. Proposals Not Meeting the Definition of Research Involving Human Subjects in Section 4.2**

The CHS office pre-reviews all applications according to the same stringent criteria outlined in this policy and procedure manual. If the CHS staff determines through a preliminary review of the CHS Application (Appendices 18, 19, 20, 21, 21a, 49b, 50a), the CHS Use of Coded Private Information or Biological Specimens form (Appendix 22), or the Determination of Human Subjects Research form (Appendix 22a) that a project does not meet the DHHS or FDA definitions of research involving human subjects in Section 4.2, the study materials are forwarded to the ORSP Director for final determination. The ORSP Director performs an additional review and may require additional information from the Investigator. Once all of the information has been provided, and the Director has made a final determination that the study does not meet the definitions of research involving human subjects in Section 4.2 the CHS staff generates a letter explaining why the project does not meet the definitions (Appendix 23). The Letter is sent by the CHS Staff to the Investigator, ordinarily within two business days of the determination. When an Investigator has completed the Use of Coded Private Information or Biological Specimens form, the application is signed by the ORSP Director as a certification that the project meets the OHRP Guidance on Research Involving Coded Private Information or Biological Specimens a letter confirming this determination (Appendix 24) is generated by CHS staff and sent to the Investigator ordinarily within two business days of the determination.

If an Investigator (or his or her staff) would like to consult with the CHS staff to determine whether a project meets the definitions of research involving human subjects as defined in Section 4.2, a copy of the complete grant/funding application must be submitted (if applicable), along with the Determination of Human Subjects Research form, as well as a list and description of all activities taking place by agents of the Faculty of Medicine and any activities taking place on Faculty of Medicine property. If there is no funding award for the research, a detailed plan (or protocol) of the proposed project will be required. CHS staff may require additional documentation (such as completion of the CHS application, Use of Coded Private Information or Biological Specimen's Form, or data collection instruments), as necessary to make an appropriate determination. CHS staff will contact the individuals as needed by phone or email to clarify any questions they may have before a determination is made.

Any time a proposed activity involves any contact with participants whether through procedures, questionnaires, surveys, interviews, focus groups, sample tissue, cell lines or any material or data that may or may not be linked to participants, a determination must be made through the CHS office about whether the activity meets the definition of research with human participants with subsequent appropriate CHS review. Self-identification by Investigators of this determination is not allowed according to Faculty of Medicine policies. If the defined research involves any of the above broad categories, Investigators should contact the CHS office for an official determination.

#### **4.4. Scientific Review**

In accordance with 45 CFR § 46.111(a)(1) and 21 CFR § 56.111(a)(1), the CHS considers whether risks to participants are minimized in research projects, in part by evaluating whether the research procedures are consistent with sound research design. The CHS review includes an assessment of the validity of the research question(s) and procedure(s), and the appropriateness of the study design. Review of the study design includes, without limitation, an evaluation of: the statistical analysis and power calculation; the adequacy of the sample size; and, where applicable, the dosage of any medication or radiation being proposed in the study. Attention is paid to the degree to which the hoped-for benefit to science and to study participants justifies the risks to participants, and to whether there is any unnecessary duplication of previous investigations in this subject area. CHS applications require the signature of the Department Head, which certifies that the proposal has scientific merit and is supported by the resources of the Department.

The CHS does not necessarily equate its scientific review to the National Institutes of Health (NIH), FDA, or Company peer review processes. Clinical research sent to the CHS may have received prior scientific review by one of the following entities:

- NIH Study Section
- FDA Review Committee
- Company Review Committees for industry-sponsored protocols
- Protocol Review by each Department Head or Department reviewing committee.

The CHS will consider these prior reviews as an indication that the scientific research design is sound, but these reviews do not release the CHS of its responsibility for scientific evaluation of the study protocol. Each protocol is pre-reviewed by CHS staff, and if, through this pre-review process, the CHS staff do not believe a CHS member has the expertise required to evaluate the scientific question or proposed research methods, the staff will alert the CHS Administrator, who will consult with the ORSP director, IO, and Chair to make a final determination, and to recommend an appropriate consultant, if necessary.

The CHS will disapprove any application that is not found to be scientifically sound, and will defer approval of a project if it requires modifications. In all circumstances, a protocol will not be approved unless it meets scientific standards, as well as ethical standards, and the risks to research participants are minimized.

##### **4.4.1. Additional Consultant for Scientific Review**

If outside scientific review has not been performed and the CHS believes it does not have the expertise required to evaluate the scientific question or proposed research methods, then the CHS will request outside scientific review by a consultant prior to before taking action on a protocol. The consultant may or may not have a Harvard affiliation. The CHS Administrator (IO, Director, or Chair) will ask the prospective consultant if s/he has any conflicts, personal, financial or professional, with the study, Investigator, or sponsor. The CHS will not accept the opinion of a consultant who has such a conflict. Upon confirmation by the prospective consultant that no

such conflict exists, the consultant will be sent the appropriate study information in order to make a determination on the scientific merit of the research project. The consultant's written evaluation will be sent to the CHS members along with the materials necessary to review the protocol at least one week before the CHS meeting and will be available during the meeting for the discussion of the study. At the request of the Reviewer or Chair, the consultant may be asked to appear at the CHS meeting if the prospective research project is particularly complicated, or if the Reviewer or Chair requests their presence; however the consultant may not vote. Determination of scientific merit will be documented on the Reviewer Sheet and key information provided by the consultant will be documented in the minutes of the meeting. The consultant's written evaluation will be maintained in the protocol file.

#### **4.5. Ethical Review**

As noted earlier in these policies, the CHS is guided in its ethical review by the Belmont Report.

Under the dictum that "bad science is bad ethics", any project found not to be scientifically sound is considered to be unethical. Consequently, any participant involvement would be unethical, as it would unfairly put the participants at risk. This risk may be as simple as having participants use their time and effort to be interviewed or as complex as being enrolled in a clinical trial.

In certain special situations a person with formal training in ethics may be contacted to offer an opinion about the ethics of a particular study. This opinion will be sent to the CHS in writing or the CHS may ask him/her to attend the meeting where the issue will be discussed.

When the CHS finds a study to be scientifically and ethically sound, the review process continues, and the CHS reviews other issues, such as level of risk, equitable selection of participants and issues surrounding consent, autonomy, safety, privacy and confidentiality, as noted elsewhere in these policies.

#### **4.6. Funding Review**

The CHS reviews all research funding applications and contracts that outline the resources and details of a study. This review ensures that the funding application and the CHS application contain the same information (i.e. study sites, research personnel, conditions of research facility, study procedures, study goals), and ensures that the Investigator has adequate resources to address any commitments to or for the participants. Grants and contracts should contain adequate resources for research participants that will cover items such as compensation or treatment for any injuries that might be incurred from the research, compensation for participation (i.e. remuneration or transportation), and translational services (for participants and/or study documents), and other items as appropriate.

#### **4.7. Investigator/Research Staff Experience**

The CHS requires that Investigators submit CVs or biosketches as well as human subjects training certificates (or confirm completion of HETHR training) for themselves and all staff who

will have responsibilities with study participants and/or data/specimens containing participant identifiers. The CHS requires this information to confirm that the Investigator and his/her staff have appropriate expertise to conduct the study and to protect the participants by safeguarding their rights and welfare, and the confidentiality of study data. CVs/ biosketches are included in the material sent to CHS members for their review. If the CHS determines that an Investigator is not qualified to conduct the study, then the CHS may request that the Department Head appoint a Co-investigator or an appropriate mentor.

The Faculty of Medicine requires Investigators to understand the responsibilities associated with conducting human studies research. Investigators must comply with federal regulations; state and local law; and Faculty of Medicine, CHS and University policies. Investigators are responsible for ensuring that their research personnel have taken the appropriate training for work with human participants. Ultimately, Investigators are responsible for protecting the rights and welfare, safety, confidentiality and privacy of the participants in their studies.

The CHS staff has developed training material and presentations about human studies research that are given to Departments upon request for faculty, students, or others. Additionally, presentations are made to post-doctoral fellows on a monthly basis. There are also seminars in the Responsible Conduct of Research given each year that are required of research fellows receiving NIH training grants, and, training programs have been established through the Sponsored Programs Administration (SPA) to educate the Departmental Administrators about the need to contact the CHS office if there are any questions relating to human studies research by Faculty members. SPA grant administrators are also instructed to notify the CHS staff if there are any questions about a human study determination on a grant.

The CHS requires that all Investigators working with human participants renew their training certification every three years. The Harvard training program for Investigators working with human participants is the Harvard Ethical Training in Human Research (HETHR) Program. The HETHR program allows for six basic modules covering research with human participants and 18 electives, each on a specific topic. The CHS may require an Investigator to take a particular elective if it is relevant to his/her research (e.g. an Investigator working with children may be required to take the module on research with children).

#### **4.7.1. Investigator Conflict of Interest**

All Investigators who are HMS and HSDM faculty, fellows or students must comply with the Faculty of Medicine Policy on Conflicts of Interest and Commitment. The Policy has separate provisions for clinical and non-clinical researchers, with greater restrictions on Investigators conducting clinical research. All Investigators whose research funding is through HMS and or HSDM also must comply with the Harvard University Government, Foundation, and Industry-Sponsored Activity Financial Disclosure Process (Appendices 25 and 26) at the time of grant submission. Investigators applying for federal Public Health Service or National Science Foundation Awards must comply with the provisions of federal regulations governing conflict of interest in research (42 CFR § 50 Subpart F, 45 CFR §§ 94 and 60, and Fed. Reg. 35820).

As a requirement of continued appointment, HMS and HSDM faculty must report conflicts on a regular basis to the Office of the Dean. The Faculty of Medicine's Office for Research Issues (ORI) oversees the identification, management and resolution of individual conflicts of interest. Under the Faculty of Medicine Conflict of Interest Policy, faculty members submit disclosure forms, either electronically or in paper copy, which are entered into a database. If potential conflicts are identified, an appropriate official contacts the faculty member. Resolution of the conflict is reported back to the ORI.

When conflicts are disclosed, they are reviewed by the Office of the Dean, in consultation with the Standing Committee on Conflicts of Interest, which is responsible for imposing appropriate conditions and limitations, sometimes including oversight mechanisms, to ensure that conflicts are appropriately eliminated, minimized and/or managed. The Investigator (and, in some circumstances, members of the research team), are consulted throughout this process, so as to ensure they are fully aware and understand how the Investigator's conflict could affect the relationship with the participants or the outcome of the research.

General awareness and understanding in the Faculty of Medicine community (including among Investigators and their research staffs) about conflict of interest issues, and how they might affect research participants or the design, oversight, conduct, outcome, or reporting of research studies, is promoted in a number of ways. All Faculty of Medicine postdoctoral researchers, prior to commencing work at HMS and HSDM, listen to a presentation on Conflicts of Interest provided by the Dean for Faculty and Research Integrity, who also makes presentations to Department faculty on conflicts in interest issues, including the review and discussion of case studies. The HETHR training contains information on conflict of interest; and conflict of interest training about potential conflicts is provided to research trainees through the required Responsible Conduct of Research Course.

The CHS Application (Appendices 18, 19, 20, 21, 21a, 49b, 50a) requires Investigators to disclose actual and potential financial conflicts of interest (including whether the Investigator has a financial interest in the sponsor or the company whose technology is being studied, and whether the Investigator may financially benefit if the study results are commercialized). Investigators are advised to call the ORI if they have any questions.

The CHS involves the ORI when a potential conflict of interest is identified with respect to a study under its review. The CHS may decide to disapprove or restrict a proposal based on a conflict of interest, even if the relationship is not prohibited under the Conflicts Policy. The CHS may not, however, disregard a conflict that is not permitted under the Conflict of Interest Policy. When conflicts are disclosed, CHS approval is deferred until the financial interest is evaluated by ORI and conflicts are satisfactorily resolved. The CHS review includes a review of any financial conflicts disclosed by an Investigator, and the management plan or resolution developed in conjunction with ORI before final approval is granted. .

#### **4.8. Research Meeting Exempt Review Categories**

All research proposals are reviewed in the office by CHS staff according to the same stringent criteria outlined in this policy and procedure document. In some instances, the CHS may

determine that a particular research project meets federal exemption categories 45 CFR § 46.101(b)(1-6), 45 CFR § 46.201(b), 45 CFR § 46.301(a), 45 CFR § 46.401(b), and 21 CFR § 50.104 (see Section 4.8.3).

#### **4.8.1. Review of Research Proposals for Exemption Criteria**

The following materials must be submitted for CHS to determine whether a research proposal meets exemption criteria (see Section 4.8.3):

- CHS Application
- Grant or funding application/contract
- IRB approvals from other institutions (and applications, when appropriate)
- Waiver requests
- HIPAA authorizations
- Consent forms
- Recruitment materials
- Study materials (including educational materials and any surveys, questionnaires or assessments)
- Communications with Investigator (to/from CHS staff and/or Reviewer)
- Reviewer Sheet

If the CHS staff determines through a preliminary review that a project meets the federal qualifications for exempt status, the study materials are forwarded to the ORSP Director (designated by the CHS to approve studies meeting exemption criteria) or CHS Chair or member for final determination. The Director (Chair or member) performs an additional review and may require additional information from the Investigator. Even when a study proposal has been identified as exempt (or as not meeting the federal definition of human subjects research; see Section 4.3), it is reviewed by the Director (Chair or member) for ethical and risk considerations including: 1) the risk/benefit ratio to participants; 2) equitable selection of participants; 3) issues of privacy; confidentiality and safety; and 4) autonomy and informed consent of the participants, as applicable.

If the Director (Chair or member) has made a final determination that a study is exempt, then the CHS staff generates a Letter of Exemption (Appendix 27), noting the applicable exemption category, and sends it to the Investigator, ordinarily within two business days of the determination. In the Letter, Investigators are notified that the exemption status is applicable to only the work outlined in the CHS Application and the grant application or contract (if any) with which it is associated. Any changes to the application or the study must be reviewed by the CHS office de novo and a determination made as to whether continuation of the appropriate exempt status is appropriate, or whether the change instead requires expedited or full CHS review.

In cases where there is ambiguity regarding exemption status, the application will be sent to the CHS Chair or member for further review. All exemptions are reported to the CHS at the next convened meeting.

Prior to acceptance of a grant or contract award involving participants in research, the Faculty of Medicine Sponsored Programs Administration (SPA) office confirms through the HIRBERT

database that a project has been approved (or determined to be exempt). The SPA office will not set up a financial account for the Investigator's award if it has not received a Letter of Exemption generated by the CHS office.

#### **4.8.2. Unacceptability of Investigator Self-Exemptions**

The CHS, and not the Investigator, must determine whether research activities qualify for exemption. The Faculty of Medicine requires that all research involving human intervention/interaction or identifiable private information as defined in these policies and procedures be subjected to CHS review.

#### **4.8.3. Exemption Criteria**

The CHS follows the federal regulations and OHRP guidance on exemption (45 CFR § 46.101(b), 45 CFR § 46.201(b), 45 CFR § 46.301(a), 45 CFR § 46.401(b) and 21 CFR § 50.104), which state:

Unless otherwise required by [federal] department or agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from [regulation under 45 CFR § 46]:

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

\*Additional criteria:

- The research does not involve prisoners as research participants.
- The research is not FDA regulated.

- (2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:

- (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and
- (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

\*Additional criteria:

- If the research involves children as participants, the activities must be limited to observation of public behavior where the Investigator does not participate in the activities being observed and to educational tests.
- The research does not involve prisoners as research participants.
- The research is not FDA regulated.

- (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 (b)(2) of this section, if:
- (i) the human subjects are elected or appointed public officials or candidates for public office; or
  - (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

\*Additional criteria:

- The research does not involve prisoners as research participants
- The research is not FDA regulated.

- (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.

\*Additional criteria:

- “Existing” means existing at the time the research is proposed
- The research does not involve prisoners as research participants
- The research is not FDA regulated.

- (5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:

- (i) Public benefit or service programs;
- (ii) procedures for obtaining benefits or services under those programs;
- (iii) possible changes in or alternatives to those programs or procedures; or
- (iv) possible changes in methods or levels of payment for benefits or services under those programs.

\*Additional criteria:

- The research does not involve prisoners as research participants
- The research is not FDA regulated.

Investigators who believe that their studies are eligible for exemption under 45 CFR § 46.101(b)(5), must forward a letter to the CHS office addressing the items noted in the OHRP guidance at <http://www.hhs.gov/ohrp/humansubjects/guidance/exmpt-pb.htm>:

- (1) 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).
- (2) The research or demonstration project must be conducted pursuant to specific federal statutory authority.
- (3) There must be no statutory requirement that the project be reviewed by an IRB.
- (4) The project must not involve significant physical invasions or intrusions upon the privacy of participants.

In addition, before making a determination about exemptions under 45 CFR § 46.101(b)(5), the CHS must consult with the DHHS funding agency as to whether the conditions stated above have been met. Both a letter from the Investigator and a letter from the DHHS agency must be submitted to OHRP by the CHS office before the exemption can be considered final.

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

\*Additional criteria:

- The research does not involve prisoners as research participants.

#### **4.8.4. Applicability of Exemption Criteria to Vulnerable Populations (45 CFR § 46 Subparts B, C and D)**

*Pregnant women, human fetuses and neonates involved in research (Subpart B):* the exemptions at 45 CFR § 46.101(b)(1) through (6) **do** apply.

\*For more information on Subpart B, please see section 11.1 of these policies and OHRP regulations at <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartb>.

*Prisoners (Subpart C):* Presently, no research involving prisoners may be exempt.

\*For more information on Subpart C, please see section 11.2 of these policies and OHRP regulations at <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartc>.

*Children (Subpart D):* The exemptions at § 46.101(b)(1) and (b)(3) through (b)(6) are applicable to children. The exemption at § 46.101(b)(2) regarding educational tests is also applicable to children. However, the exemption at § 46.101(b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research involving children, except for research involving observation of public behavior when the Investigator(s) do not participate in the activities being observed.

\*For more information on Subpart D, please see section 11.3 of these policies and OHRP regulations at <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartd>.

#### **4.9. Research Meeting Expedited Review Categories**

Research proposals meeting federal categories for expedited review (see Section 4.9.2.2) may be eligible for an expedited review process. Expedited reviews are performed by the CHS chair or the Chair's designated CHS members (herein referred to as the "Reviewer"). In accordance with 45 CFR 46.110(b), the Reviewer "may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research." The same materials provided for the convened CHS review (initial and continuing reviews, and modifications to approved research; see Section 4)

are required for expedited review, and are sent to Primary Reviewers for their review of the research.

#### **4.9.1. Review of Research Proposals for Expedited Criteria**

All research proposals are pre-reviewed in the office by CHS staff according to the same stringent criteria outlined in this policy and procedure document. In some instances, the CHS may determine that a particular research project meets federal expedited review criteria set forth in 45 CFR § 46.110(a)-(d), and to make this determination, the same materials indicated in Section 4 must be submitted for CHS review. Expedited procedures may be used for initial and continuing review of research, and modifications to previously approved research under the criteria outlined in the following sections.

#### **4.9.2. Categories of Research that may be Reviewed through an Expedited Review Procedure**

OHRP guidance at <http://www.hhs.gov/ohrp/humansubjects/guidance/expedited98.htm> allows for expedited procedures to review minor modifications (modifications are minor if they involve the addition of no more than minimal risk and are limited to the addition of procedures listed in categories (1)-(7) of categories of research that can be approved by the expedited procedure) to previously approved research. The following conditions and categories of research may be reviewed by an expedited procedure:

##### **4.9.2.1. Applicability**

- (A) Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR § 46.110 and 21 CFR § 56.110. The activities listed 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.
- (B) The categories in this list apply regardless of the age of subjects, except as noted.
- (C) 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.
- (D) The expedited review procedure may not be used for classified research involving human subjects.

(E) IRBs are reminded that 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.

(F) Categories one (1) through seven (7) pertain to both initial and continuing IRB review.

#### **4.9.2.2. Research Categories**

- (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 § 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 § 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<sup>1</sup>, 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.
- (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.

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<sup>1</sup> Children are defined in the HHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." [45 CFR § 46.402\(a\)](#).

- (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 HHS regulations for the protection of human subjects. 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 HHS regulations for the protection of human subjects. 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.
- (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.

#### **4.9.3. Reviewer Determination**

Upon making an initial determination that a study may qualify for expedited review under an appropriate category (or categories) the CHS staff will provide all of the research materials to the

Reviewer. The materials will be accompanied by a Reviewer Sheet (Reviewer sheets are used for initial and continuing reviews of research, as well as review of modifications to approved research projects, for convened CHS meetings, as well as expedited review procedures) and a Review Confirmation Sheet (RCS, Appendix 28a) for the Reviewer to complete. Reviewers may only approve or require modifications to the protocol or protocol materials to secure approval (disapprovals of research must be determined by the convened CHS).

All research proposals approved using expedited review procedures in a given month are reported via spreadsheet (along with the exemptions, ceded reviews, and closed studies) to the CHS at each convened meeting.

#### **4.9.4. When there are Contingencies for Approval**

If contingencies exist for the approval of the study, the CHS staff responsible for the file will send these contingencies in writing to the Investigator, ordinarily within five business days. The Investigator will be responsible for satisfying the Reviewer's contingencies and will communicate with CHS staff until the contingencies appear to have been satisfactorily addressed. The CHS staff will report the Investigator's actions/changes to the Reviewer. When, in the opinion of the Reviewer, the contingencies have been satisfied, a Report on Action (ROA, Appendix 28) will be generated. Additionally, a study may be approved with contingencies (using this same procedure) when the convened CHS requests specific modifications that may be approved by expedited procedures. This is stated at the meeting, and documented in the minutes.

In all cases, if the Reviewer determines that the study or the participants would be better served by a full CHS review, complete study materials will be sent to the next appropriate convened CHS meeting.

#### **4.9.5. Notification to Investigators**

CHS staff will send the ROA to the Investigator, along with any stamped or approved study documents, such as the consent form, recruitment materials, or study instruments. The approved consent form will contain the CHS stamp (unless it has already been stamped approved by another institution's IRB), validating it for the period of approval. The period of approval is one year minus one day (364 days), unless otherwise noted on the ROA and accompanying documentation.

Included within the ROA is the document entitled "Responsibilities of the Investigator" (Appendix 29) which serves as a reminder to the Investigator to report adverse events and unanticipated problems, to seek approval of any modifications to the research (or research materials) prior to implementation, and to seek re-approval in a timely manner. The Investigator is responsible for using only the current, validated consent form with research participants. It is the responsibility of the Investigator or SPA to forward notification of approval to appropriate funding agencies.

#### **4.9.6. CHS Approvals and Release of Funds for Research**

The SPA office will only set up a financial account for an Investigator's award if CHS approval is documented by a current (unexpired) ROA from the CHS office, or if there is notification of current CHS approval in HIRBERT.

#### **4.10. Research Requiring Full Committee Review**

As with all other research projects submitted to the CHS office, a preliminary review of the application and supporting materials is performed by CHS staff. CHS staff are responsible for communicating with the Investigator in the same manner as other projects, and assisting them in preparation of materials to be reviewed at a convened CHS meeting (also referred to as full CHS review).

##### **4.10.1. Research Involving More than Minimal Risk**

All research proposals that may involve more than minimal risk (see Section 4.2) to participants, or that do not fit within exempt or expedited review criteria, are accorded full CHS review.

##### **4.10.2. Proposals Not Involving More than Minimal Risk, but that Require Full Committee Review**

On occasion, studies involving minimal risk procedures are brought for full CHS review, usually those involving vulnerable populations (see Section 11), sensitive topics or stigmatized conditions, or international sites. There also may be studies that, while technically falling within an exempt or expedited review category, are determined by the CHS Chair or members to warrant full CHS review.

##### **4.10.3. Document Distribution**

Documents for initial, full CHS review are sent to all CHS members who will participate in the meeting, ordinarily seven days prior to the meeting. The following documents are provided to attending CHS members for each study to be reviewed at the convened meeting:

- Human Studies Application
- Grant application or funding application/contract
- The full protocol
- The sponsor protocol (if applicable)
- The complete DHHS-approved protocol (when one exists)
- The DHHS-approved sample consent document (when one exists)
- The Investigator's brochure (or package insert or pages from the Physician's Desk Reference, if a marketed drug)
- IRB approvals from other institutions (and applications, when appropriate)
- Waiver requests
- HIPAA authorizations
- Consent forms
- Recruitment materials

- Study materials (including educational materials and any surveys, questionnaires or assessments)
- Communications with Investigator (to/from CHS staff and/or Reviewer)

#### **4.10.4. CHS Review Procedures**

At the start of each meeting, the Chair takes attendance to assure a quorum (at least one half of the membership, plus one), and the CHS Administrator keeps track of the quorum and any changes in the quorum to assure a valid vote throughout the meeting (voting does not take place without a valid quorum). The Chair reviews the agenda with the CHS members and asks the members whether they have any conflicts of interest with any study to be reviewed at the meeting and if so, reminds them to leave the room for the discussion and vote on that study. CHS members are reminded that the discussions during the meeting and the meeting materials are confidential and should not be discussed outside of the meeting or outside their role as CHS members.

The Primary Reviewer summarizes the study (i.e. purpose, procedures, risks, and benefits), for which he or she is responsible, indicating any issues of particular concern, and initiating discussion. If a Secondary Reviewer has been assigned, the Secondary Reviewer provides any additional information not noted by the Primary Reviewer. While the Primary Reviewer is responsible for presenting the study at the meeting, all CHS members in attendance are expected to thoroughly review the materials sent to them for each study in order to discuss the protocol at the meeting. Files of protocols and copies of minutes are brought to convened meetings, should there be any questions requiring additional information (CHS members may also request from CHS staff, information from the files or minutes to assist in their review prior to the meeting). After the discussion, the Chair summarizes any remaining issues, asks for a motion, a second on the motion, and a hand vote of those in favor, those opposed and those abstaining from the vote. The vote is then announced and recorded by the CHS Administrator on the RCS (Appendix 28a) for the Chair to sign at the end of the meeting.

#### **4.10.5. CHS Determinations**

CHS members make determinations, or actions, in the form of a vote, or they may abstain from a vote on a study. There must be a quorum of CHS members eligible to vote on a study at the meeting (either in person or on a telephone conference call) for a vote to be valid.

##### **4.10.5.1. Voting Validity**

In order for a motion to pass, it must be voted for by a majority, at least one half plus one, of CHS members present at the meeting (i.e. if attendance is 14, passing is 8; if attendance is 15, passing is 9). Votes include those in favor, against, or abstaining from a motion. Abstaining votes do not count against the quorum for the meeting. However, those who have declared a conflict of interest cannot vote and therefore *are* counted against the quorum.

##### **4.10.5.2. Participation by Telephone**

Whenever possible, CHS members are encouraged to be physically present at the meeting. However, there are times when circumstances change and occasionally a member cannot be physically present. In such a circumstance, the CHS member may still participate in the discussion and vote via conference call, as long as s/he received the materials in ample time to review them before the meeting, and as long as s/he is able to hear and be heard for the discussion and vote. Participation in meetings via conference calls is noted in the meeting minutes.

### **4.10.5.3. CHS Actions and Notifications**

#### **4.10.5.3.1. Approval**

Approval means that all aspects of the study have been reviewed and found to be scientifically, methodologically, and ethically sound. When a study is approved, the ROA (Appendix 30) is sent to the Investigator with any stamped/approved study materials (such as consent forms, recruitment materials and study instruments) by CHS staff, ordinarily within five business days of the meeting. Included within the ROA is the document entitled “Responsibilities of the Investigator” (Appendix 29) which serves as a reminder to the Investigator to report unanticipated problems, to seek approval of any modifications to the research (or research materials) prior to implementation, and to seek re-approval in a timely manner. Approvals and approved study materials are valid for one year minus one day (364 days) of the CHS meeting in which the protocol was reviewed, unless otherwise specified on the ROA.

Once the Investigator receives the ROA and signed/stamped approved study materials, s/he may commence study activities.

It is the responsibility of the Investigator to forward notification of approval to appropriate funding agencies.

#### **4.10.5.3.2. Contingent Approval**

Contingent approval means that the study requires only specific minor revisions or requires yes/no concurrence by the Investigator. A letter or email will be sent to the Investigator by CHS staff outlining the issues requiring confirmation or concurrence, ordinarily within five business days of the CHS meeting. Minor revisions may include: a change that does not alter the risk:benefit analysis of the study, affect the safety of participants, include the addition of study procedures, interactions or interventions, alter in any way the scientific integrity of the study, or include a procedure or vulnerable population for which expedited review is not permissible.

A study that has been approved with contingencies may be fully approved when the concurrences and/or specific minor revisions have been made by the Investigator and confirmed/approved by the Primary Reviewer and/or Secondary Reviewer or Chair. The met contingencies do not necessarily need to be reviewed again by the full CHS, but this should be specified at the meeting in which the contingencies are determined. Otherwise, any contingencies, concurrences/modifications, will be reviewed at the next convened meeting. If the concurred/revised materials are satisfactory, an ROA indicating full CHS approval will be sent to

the Investigator as outlined in the approval section, above. The date of approval is that of the CHS meeting minus one day.

When, in the opinion of the Reviewer, an Investigator fails to respond adequately to the stipulated requirements of the CHS, the CHS will reconsider the matter at the next full CHS meeting. Investigators who disagree with the requested revisions may present their justifications in writing to the CHS to review at the next full CHS meeting.

#### **4.10.5.3.3. Deferred Approval**

Deferred approval means that the study requires more than simple minor revisions or modifications before it can be approved by the CHS. A letter or email will be sent to the Investigator by CHS staff inclusive of the reasons/justification for the CHS's decision and suggestions to further develop the study design and/or study materials. The modifications must be reviewed at a full CHS meeting. When a deferred study has been revised and the materials returned to the full CHS meeting, the study shall be reviewed as though it were a new study.

Studies that receive a deferral should be resubmitted to the CHS within six months, unless the issue delaying the approval is not within the Investigator's control, such as Investigational New Drug (IND) or Investigational Device Exemption (IDE) applications to the FDA. If study modifications and a revised CHS application are not resubmitted within six months of the deferral, the CHS office will contact the Investigator to determine whether the study should be closed. If no information is forthcoming, the CHS office may decide to close the file and will notify the Investigator of its decision.

#### **4.10.5.3.4. Disapproved**

Disapproved means that the study is not scientifically, methodologically, and/or ethically sound and the CHS will not approve the study as designed. The CHS staff will send a letter to the Investigator, ordinarily with a copy to the Department Chair (or mentor if a student project) and SPA, indicating the reasons for its decision. In its letter, the CHS will afford the Investigator the opportunity to respond in person at a convened meeting, or the Investigator may choose to respond in writing and the response will be reviewed at a convened meeting.

### **4.11. Research Requiring Review More Often than Annually**

While most approvals are granted for one year minus one day (364 days), there are projects that may require more frequent review. For such projects (most often involving more than minimal risk for participants), the CHS will consider whether more frequent review is warranted to ensure adequate protection of the rights and welfare of research participants and will document its determination in the minutes of the meeting. In determining the frequency of review, the CHS will consider carefully the risk:benefit analysis especially with the participation of vulnerable populations (see Section 11) and other reasonable factors including but not limited to issues that may be sensitive to the public. The ROA specifies the required frequency for continuing review of the study.

#### **4.12. Research Monitoring**

Separate from the IRB Quality Assurance Coordinator (see Section 2.8.1.1.1), the CHS has the authority to appoint one or more individuals to observe the consent process and/or the research and to report back to the CHS with any findings. The CHS shall appoint such an individual whenever it determines, based on information available (such as reports of adverse events or unanticipated problems involving risks to participants or others, deficiencies noted in the CHS office files, reports or complaints from study personnel or participants, media or scholarly reports of research activity) that monitoring is in the best interests of the participants and/or integrity of the study. The CHS also may request that an Investigator design an instrument to document the understanding of consent by a (potential) research participant. The CHS may request that this documentation be provided for its review at any time during the study.

#### **4.13. International or Off-Site Research and Knowledge of the Local Research Context**

The CHS is required to have knowledge of the local research context, whether domestic or international, (<http://www.hhs.gov/ohrp/humansubjects/guidance/local.htm>) in order to provide a thorough review, to understand particular risks and benefits of the study population, and the relevance, customs and cultural significance of study procedures to the community in which the research is taking place. All sites are required to have a local IRB or Independent Ethics Committee (IEC) approval. When federal funds are supporting the research, the local IRB or IEC must have a FederalWide Assurance of compliance with OHRP.

In the event that non-federal funds are supporting the research, IRB or IEC approval is still required, unless there is no such board at the site where the research is taking place. While some less populated communities may not have such a board, most communities have a structure (council or local leader) in place that approves the activities of that community. In addition to the approval of this committee or person, a letter of support from the local site (such as a school principal or superintendent, or a clinic director) where the research activities will be taking place should be obtained by the Investigator and provided to the CHS. The letter should include information pertaining to the appropriateness of the study to the local community, any required changes to the study, and a review and approval of the consent document, whenever possible. Letters not provided in English must be translated into English for CHS review and a Translation Attestation Form (Appendix 18a) signed by the Investigator must accompany the letter.

Depending on the research or the risks (or level of risks) to participants and the support from the local community, the CHS may also request that someone (other than the Investigator) with special knowledge of the setting either review a particular protocol, or attend a convened CHS meeting to provide the CHS with recommendations based on his/her expertise. This person must be familiar with the customs, practices, or standards of care (and language, whenever possible) where the research will be taking place.

### **5. Continuing Review of Research**