



**RESEARCH FOR WHICH REVIEW BY THE
DUKE UNIVERSITY HEALTH SYSTEM
HUMAN RESEARCH PROTECTION PROGRAM IS REQUIRED**

10/2/2008

All research involving human subjects must be reviewed by the DUHS HRPP prior to initiation of the research when it:

- is sponsored by DUHS, including all of its institutional components; OR
- is conducted by or under the direction of any employee or agent of DUHS (including a student, resident or fellow*) in connection with his or her institutional responsibilities, regardless of funding source (or lack thereof), and regardless of the performance site**; OR
- is conducted by or under the direction of any employee or agent of DUHS using any DUHS property or facility; OR
- utilizes DUHS non-public information*** to identify or contact human subjects

unless:

- the research will be reviewed by an IRB designated on the DUHS Federal-wide Assurance and an IRB Authorization Agreement is in place; OR
- the DUHS IRB determines that:
 - the research is not eligible for exemption from IRB review, and
 - the research meets one or more of the examples of not being engaged in human subjects research listed in OHRP guidance on “Engagement of Institutions in Research”, dated 1/26/99 and found at:
<http://www.hhs.gov/ohrp/humansubjects/assurance/engage.htm>
- OR
- the Duke faculty or staff member plans to conduct research with human subjects solely at the Durham Veterans Administration Medical Center (DVAMC), and the investigator provides documentation of DVAMC IRB approval of that research****; OR
- the research meets the criteria for exemption from review prior to the initiation of an emergency use of a test article.

* Duke medical students, residents or fellows who are involved in research led by others at Duke must be listed as Key Personnel on the IRB submission. Duke medical students, residents or fellows who are involved in research led by others at an unaffiliated site may satisfy their responsibilities to the IRB by meeting the requirements of the “Policy and Procedure for Duke Trainees Engaged in Research Involving Human Subjects at a Site Other Than Within DUHS”. This policy, appropriately modified, applies to DUHS residents and fellows who do research involving human subjects while away from DUHS as a part of their

training program. It also applies to DUSOM faculty members not on sabbatical or leave who do such research while away from DUHS.

** If the performance site is not a DUHS facility, the DUHS IRB will oversee the research activity upon execution of an appropriate agreement between DUHS and the collaborating investigator unless an alternate written agreement is in place that cedes authority to another IRB. Note that such oversight may occur as described above*.

*** In this case, the IRB reviewer(s) may conclude that the use of the non-public information does not lead to the user being engaged in research involving human subjects as defined by OHRP.

**** If the Duke investigator plans to conduct a portion of the research using a Duke facility, the research will be reviewed by the DUHS IRB in compliance with all applicable federal regulations/guidelines and DUHS policies.

The IRB will review and approve research conducted outside the United States by DUHS employees or students, even if the foreign research activity has no U.S. federal funding. The IRB may approve such non-U.S. funded research, provided it determines that: (a) the research conforms to proper codes of ethics (such as the Declaration of Helsinki and/or the Belmont Report), and (b) the research is approved by the foreign research site's ethical review authority. Requirements for the informed consent process will follow the laws and customs of the country in which the research is being conducted. If a U.S. Department or Agency funds the research, then the IRB would expect the foreign research site to have an approved Federal-wide Assurance and meet all applicable DHHS and FDA regulations and guidance.

IRB review and approval of a research project must occur before the research begins, and continuing assessment by the IRB must occur during the life of the research study through the process of periodic continuing review of the research.

The IRB, represented by its Chairs, Vice-Chairs or Executive Director, must make a series of determinations before it decides whether to consider an activity to be research involving human subjects that requires IRB approval before study initiation. The reviewer may use the "Checklist to Determine if an Activity is Subject to IRB Review" to assist him/her in this process.

For an activity to be eligible for IRB approval at the time of initial review, the IRB must determine in the following order that:

- (1) The activity involves research;
- (2) The activity involves research with human subjects;
- (3) The activity is not eligible for exemption from IRB review;
- (4) The institution and its investigators/staff will be engaged in research involving human subjects.

Research Involving Human Subjects: 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 FDA .

Research (DHHS) [45 CFR 46.102(d)] - a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

Human Subject (DHHS) [45 CFR 46.102(f)] - a living individual about whom an investigator (whether professional or student) conducting research obtains data through intervention or interaction with the individual, or identifiable private information.

- “Intervention” as defined by DHHS regulations means both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject’s environment that are performed for research purposes.
- “Interaction” as defined by DHHS regulations means communication or interpersonal contact between investigator and subject.
- “Private information” as defined by DHHS regulations means information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).
- “Identifiable information” 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).

Clinical Investigation (FDA) [21 CFR 56.102(c)] - 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 act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the 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 deemed to be synonymous for purposes of this part.

- “Experiments that must meet the requirements for prior submission to the Food and Drug Administration under section

505(i) of the Federal Food, Drug, and Cosmetic Act” means any use of a drug other than the use of an approved drug in the course of medical practice. [21 CFR 312.3(b)]

- “Experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 520(g) of the Federal Food, Drug, and Cosmetic Act” means any activity that evaluates the safety or effectiveness of a device. [21 CFR 812.2(a)]
- Any activity in which results are being submitted to or held for inspection by FDA as part of an application for a research or marketing permit is considered to be FDA-regulated research. [21 CFR 50.3(c), 21 CFR 56.102(c)]

Human Subject (FDA) [21 CFR 56.102(e); 21 CFR 812.3(p)] - an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient. For research that evaluates the safety or effectiveness of a device, the definition includes a human on whom or on whose specimen an investigational device is used. A subject may be in normal health or may have a medical condition or disease.

Note that the Privacy Rule (HIPAA), including its research provisions, applies to both living and dead people, and the research provisions apply when the DHHS definition of research (45 CFR 46.102(d)) is met.

The IRB Chair/Vice-Chair/Executive Director reviews the proposed activity to determine and document whether the activity meets the DHHS definition of *research* (45 CFR 46.102(d)); and the activity meets the DHHS definition of *human subject* (45 CFR 46.102(f)); or the activity meets the FDA definition of *clinical investigation (or research)* (21 CFR 50.3(c) and 21 CFR 56.102(c)), and the activity meets the FDA definition of *human subject* (21 CFR 50.3(g) and 21 CFR 56.102(e)). When the FDA definitions are met, the activity is Research Involving Human Subjects that is FDA regulated. If the DHHS definitions are met, the activity is Research Involving Human Subjects that is DHHS regulated. If both sets of definitions are met, the activity is Research Involving Human Subjects and is both DHHS- and FDA-regulated.

In order for the IRB Chair/Vice-Chair/Executive Director to make these determinations, the person proposing to conduct the activity must submit by email or via the e-IRB a description of proposed activities that is sufficient for the reviewer to assess whether or not the proposed activities meet the regulatory definitions of research involving human subjects.

When the Chair/Vice-Chair/Executive Director determines that the activity is Research Involving Human Subjects, s/he further determines whether the institution is engaged in research. The IRB Chair/Vice-Chair/Executive Director

uses the OHRP guidance “Engagement of Institutions in Research” to determine whether the institution and its investigators would be engaged in research and the research subject to DUHS IRB review. At any point in this process, the IRB Chair/Vice-Chair/Executive Director may request additional information from the PI to make the determination. If still unclear, the Chair/Vice-Chair/Executive Director may contact OHRP or FDA officials for guidance.

Some activities, such as developing a case report or a limited case series (<4 cases) for publication, or quality improvement activities that do not meet the definition of research, or research involving deceased individuals (see Decedent Research under policy guidance on the Privacy Rule [HIPAA]), are not human research according to OHRP and FDA.

When the IRB Chair/Vice-Chair/Executive Director determines that the activity does not meet the definition of Research Involving Human Subjects, the Investigator is notified in writing that the activity does not meet the definition of Research Involving Human Subjects, and that the activity does not require further IRB consideration. Investigators are provided with the basis for the determination and are informed that they may not make changes to the activity without first reviewing the changes with the IRB Chair/Vice-Chair/Executive Director to determine whether the changes are consistent with the determination. If the changes would require that the activity is now subject to IRB review, the investigator must resubmit the research for initial review as described elsewhere in this policy.

When the activity is determined to be Research Involving Human Subjects, the investigator must submit the research for initial review as described elsewhere in this policy.

(3) The criteria for *Exemption from IRB Review according to OHRP (45 CFR 46.101(b) (1)-(6))*:

Unless otherwise required by 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 this policy:

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

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

(i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and

- (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the 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 (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.
- (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 department or agency heads, and which are designed to study, evaluate, or otherwise examine:
- (i) Public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.
- The program under study must deliver a public benefit (e.g., financial or medical benefits as provided under the Social Security Act) or service (e.g., social, supportive, or nutrition services as provided under the Older Americans Act).
 - The research or demonstration project must be conducted pursuant to specific federal statutory authority.
 - There must be no statutory requirement that the project be reviewed by an IRB.
 - The project must not involve significant physical invasions or intrusions upon the privacy of participants.
 - The exemption must have authorization or concurrence by the funding agency.
- (6) Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the 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.

The exemptions 45 CFR 46.101(b)(1-6) do not apply to research involving prisoners, as stated in 45 CFR 46 Subpart C. The exemptions 45 CFR 46.101(b)(1-5) cannot be applied to FDA regulated research. The exemption 45

CFR 46.101(b)(2) does not apply to research involving children, as stated in 45 CFR 46 Subpart D, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed and research involving the use of educational tests.

The criteria for *Exemption from IRB Review according to FDA (21 CFR 56.104)*:

Activities involving drugs or medical devices will not be eligible for exemption from DUHS IRB review unless the activity falls within 21 CFR 56.104, or the activity involves the use of an FDA approved drug or device in the course of medical practice. Activities for which the data will be submitted to or held for inspection by the FDA for regulatory purposes are not eligible for exemption from IRB review.

The following categories of clinical investigations are exempt from the requirements of this part for IRB review:

(a) Any investigation which commenced before July 27, 1981 and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigation remains subject to review of an IRB which meets the FDA requirements in effect before July 27, 1981.

(b) Any investigation commenced before July 27, 1981 and was not otherwise subject to requirements for IRB review under Food and Drug Administration regulations before that date.

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

(d) Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the 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.

FDA exemption categories (a) – (c) cannot be applied to activities that meet the DHHS definition of “research” and involve “human subjects”.

Note that 45 CFR 46.101(b)(6) and 21 CFR 56.104(d) are largely identical with the exception that 21 CFR 56.104(d) is only an exemption from 21 CFR 56 (i.e., the requirement for IRB review) and is not an exemption from 21 CFR 50 (i.e., the requirement to obtain informed consent in accordance with and to the extent required by 21 CFR 50.)

The IRB Chair/Vice-Chair/Executive Director is responsible for reviewing and determining whether the research is exempt from 45 CFR 46 and/or 21 CFR 56. He/she will use the “Checklist to Determine If Research May Be Declared

Exempt from IRB Review” for assistance in making this determination. If he/she finds that the information provided by the investigator is insufficient to determine whether the proposed research meets the criteria for exemption, the investigator may be asked to complete the “Exempt Research Project Summary”.

As part of this review, the IRB Chair/Vice-Chair/Executive Director will use the “Checklist to Determine If Research May Be Declared Exempt from IRB Review” to consider whether the research meets DUHS standards for informed consent, subject privacy and the confidentiality of the subject’s data even if the Chair/Vice-Chair/Executive Director concludes that the research meets the criteria for exemption from IRB review. The IRB Chair/Vice-Chair/Executive Director uses a review sheet to indicate whether or not the research is exempt from IRB review. If the IRB Chair/Vice-Chair/Executive Director determines that the research is exempt from the requirements of 45 CFR 46 and/or 21 CFR 56, continuing review will be required every three years unless changes are made to the research that affect the exemption status and prompt the requirement for IRB protocol submission and subsequent IRB review.

The IRB Chair/Vice-Chair/Executive Director may request additional information from the PI to make these determinations. If the research does not meet the criteria for exemption, the protocol is reviewed through an expedited procedure or by full board review at a convened meeting of the IRB, as appropriate to the research activities.

Investigators are notified in writing that the research is exempt from periodic continuing review or further IRB consideration until 3 years from the declaration of exemption, at which time the investigator must resubmit his/her request for exemption from IRB review, or notify the IRB that all research activities have ended. Investigators are also notified that they may not make changes to the research activity without first discussing the changes with the IRB Chair/Vice-Chair/Executive Director to determine whether the changes prompt reconsideration of the activity’s exempt status. If the activity no longer meets the criteria for exemption, the investigator must resubmit the activity for review by the IRB at a convened meeting or through the use of the expedited review procedure.

(4) The institution and its investigators/staff will be *engaged in research* involving human subjects if their non-exempt involvement includes the following:

- (1) An institution and its investigators/staff are automatically considered to be "engaged" in human subjects research whenever it receives a direct HHS award to support such research. In such cases, the awardee institution bears ultimate responsibility for protecting human subjects under the award.
- (2) Institutions whose employees or agents intervene with living individuals by performing invasive or noninvasive procedures for

research purposes (e.g., drawing blood; collecting other biological samples; dispensing drugs; administering other treatments; employing medical technologies; utilizing physical sensors; utilizing other measurement procedures).

- (3) Institutions whose employees or agents intervene with living individuals by manipulating the environment for research purposes (e.g., controlling environmental light, sound, or temperature; presenting sensory stimuli; orchestrating environmental events or social interactions; making voice, digital, or image recordings).
- (4) Institutions whose employees or agents interact with living individuals for research purposes (e.g., engaging in protocol-dictated communication or interpersonal contact; conducting research interviews; obtaining informed consent). (See Example (B)(3) below for certain informational activities that do not constitute "engagement" in research and do not require an Assurance.)
- (5) Institutions whose employees or agents release individually identifiable private information, or permit investigators to obtain individually identifiable private information, without subjects' explicit written permission (e.g., releasing patient names to investigators for solicitation as research subjects; permitting investigators to record private information from medical records in individually identifiable form). (However, see Example (B)(5) regarding release of such information with subjects' prior, written permission, and Example (B)(6) regarding release of such information to State Health Departments.)
- (6) Institutions whose employees or agents obtain, receive, or possess private information that is individually identifiable (either directly or indirectly through coding systems) for research purposes (e.g., obtaining private information from medical records in an individually identifiable form). (However, see Examples (B)(7) and B(8) for certain activities involving the release of information and/or specimens to investigators in non-identifiable form.)
- (7) Institutions whose employees or agents obtain, receive, or possess private information that is individually identifiable (either directly or indirectly through coding systems) for the purpose of maintaining "statistical centers" for multi-site collaborative research. Where institutional activities involve no interaction or intervention with subjects, and the principal risk associated with institutional activities is limited to the potential harm resulting from breach of confidentiality, the Institutional Review Board (IRB) need not review each collaborative protocol. However, the IRB should determine and document that the statistical center has sufficient mechanisms in place to ensure that (i) the privacy of subjects and the confidentiality of data are adequately maintained, given the sensitivity of the data involved; (ii) each collaborating institution holds an applicable OPRR-approved Assurance; (iii) each protocol is reviewed and approved by the IRB at the collaborating institution prior to the enrollment of subjects; and (iv)

informed consent is obtained from each subject in compliance with HHS regulations.

- (8) Institutions whose employees or agents maintain "operations centers" or "coordinating centers" for multi-site collaborative research. Where institutional activities involve no interaction or intervention with subjects, the IRB need not review each collaborative protocol. However, the IRB should determine and document that the operations or coordinating center has sufficient mechanisms in place to ensure that (i) management, data analysis, and Data Safety and Monitoring (DSM) systems are adequate, given the nature of the research involved; (ii) sample protocols and informed consent documents are developed and distributed to each collaborating institution; (iii) each collaborating institution holds an applicable OPRR-approved Assurance; (iv) each protocol is reviewed and approved by the IRB at the collaborating institution prior to the enrollment of subjects; (v) any substantive modification by the collaborating institution of sample consent information related to risks or alternative procedures is appropriately justified; and (vi) informed consent is obtained from each subject in compliance with HHS regulations.
- (9) Institutions receiving a direct HHS award to conduct human subjects research, even where all activities involving human subjects are carried out by a subcontractor or collaborator (e.g., a small business receives a HHS award to design a medical device at its own facility and contract with a medical clinic to test the device with human subjects; a foundation receives a HHS award on behalf of an affiliated institution that will actually conduct the human subjects research).
- (10) Institutions whose employees or agents are involved in 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 act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the 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, or is a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control.

The institution and its investigators/staff will not be engaged in research involving human subjects if their involvement is limited to the following:

- (1) Institutions whose employees or agents act as consultants on research but at no time obtain, receive, or possess identifiable private information (e.g., a consultant analyzes data that cannot be linked to individual subjects, either directly or indirectly through coding systems, by any member of the research team).

- a. Should a consultant access or utilize individually identifiable private information while visiting the research team's institution, the consultant's activities become subject to the oversight of the research team's Institutional Review Board (IRB). However, the consultant's institution is not considered to be "engaged" in the research and would not need an Assurance.
 - b. Should a consultant obtain "coded" data for analysis at the consultant's institution, the consultant's institution is considered "engaged" in human subjects research, and would need an Assurance, unless a written agreement unequivocally prohibits release of identifying codes to the consultant.
- (2) Institutions whose employees or agents (i) perform commercial services for the investigators (or perform other genuinely non-collaborative services meriting neither professional recognition nor publication privileges), and (ii) adhere to commonly recognized professional standards for maintaining privacy and confidentiality (e.g., an appropriately qualified laboratory performs analyses of blood samples for investigators solely on a commercial basis).
- (3) Institutions whose employees or agents (i) inform prospective subjects about the availability of research; (ii) provide prospective subjects with written information about research (which may include a copy of the relevant informed consent document and other IRB-approved materials) but do not obtain subjects' consent or act as authoritative representatives of the investigators; (iii) provide prospective subjects with information about contacting investigators for information or enrollment; or (iv) obtain and appropriately document prospective subjects' permission for investigators to contact them (e.g., a clinician provides patients with literature about a research study, including a copy of the informed consent document, and tells them how to contact the investigator if they want to enroll; a clinician provides investigators with contact information about potential subjects after receiving explicit permission from each potential subject).
- (4) Institutions (e.g., schools, nursing homes, businesses) that permit use of their facilities for intervention or interaction with subjects by research investigators (e.g., a school permits investigators to test students whose parents have provided written permission for their participation; a business permits investigators to solicit research volunteers at the worksite).
- (5) Institutions whose employees or agents release identifiable private information to investigators with the prior written permission of the subject (e.g., with written permission of the subject, a clinician releases the subject's medical record to investigators).

- (6) Institutions whose employees or agents release identifiable private information or specimens to a State or Local Health Department or its agent for legitimate public health purposes within the recognized authority of that Department. However, utilization of such information or specimens by Department investigators for research purposes would constitute engagement in research, and would require an Assurance from the Department.
- (7) Institutions whose employees or agents release information and/or specimens to investigators in non-identifiable (i.e., non-linkable) form, where such information/specimens have been obtained by the institution for purposes other than the investigators' research (e.g., nursing home employees provide investigators with a data set containing medical record information, but the data set contains no direct or indirect identifiers through which the identity of individual subjects could be ascertained, either by the investigators or by nursing home personnel; a hospital pathology department releases excess tissue specimens and relevant medical record information to investigators, but these materials include no direct or indirect identifiers through which the identity of individual subjects could be ascertained, either by investigators or by hospital personnel, including the pathology department; consistent with applicable law or recognized authority, local hospitals or health departments permit State or Local Health Department investigators to access information for research purposes, but the investigators record no direct or indirect identifiers through which the identity of individual subjects could be ascertained, either by the investigators or by local hospital or health department personnel.)
- (8) Institutions whose employees or agents receive information or specimens for research from established repositories operating in accordance with (i) an applicable OPRR-approved Assurance; (ii) OPRR guidance (see: <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/reposit.htm>); and (iii) written agreements unequivocally prohibiting of release of identifying information to recipient investigators.
- (9) Institutions (or private practitioners) whose clinical staff provides protocol-related care and/or follow-up to subjects enrolled at distant sites by clinical trial investigators in OPRR-recognized Cooperative Protocol Research Programs (CPRPs). In such cases, (i) the CPRP clinical trial investigator (consistent with a registered investigator as defined in Section 14.1 of the NCI Investigator's Handbook) retains responsibility for oversight of protocol related activities; (ii) clinical staff may not accrue subjects or obtain informed consent for research

participation; (iii) clinical staff may only provide data to the investigator in accord with the terms of informed consent; and (iv) the informed consent document should state that such data are to be provided by clinical staff as directed by the investigator.