DUKE UNIVERSITY HEALTH SYSTEM
Human Research Protection Program

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

06/10/2026

This document provides guidance to Duke investigators in determining which activities require DUHS HRPP/IRB review.

Definitions

Research: HHS (Health and Human Services) regulations define research as a *systematic investigation*, including research development, testing, and evaluation, designed to develop or contribute to *generalizable knowledge*. (45 CFR 46.102(l))

> **Systematic Investigation:** An activity that involves a prospective plan that incorporates data collection (quantitative or qualitative) and data analysis to answer a question.
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> **Generalizable Knowledge:** Activities designed to develop or contribute to generalizable knowledge are those designed to draw conclusions, inform policy, or generalize findings beyond a single individual or an internal program. The intent to develop or contribute to generalizable knowledge makes an activity research – it does not need to be published or presented to meet this standard.

The following activities are deemed NOT to be research:

(1) Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.

(2) Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the

course of an event or crisis that threatens public health (including natural or man-made disasters).

(3) Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.

(4) Authorized operational activities (as determined by the funding/sponsoring federal agency) in support of intelligence, homeland security, defense, or other national security missions.

Clinical Investigation: 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. 21 CFR 56.102(c)

Human Subject: HHS regulations define a Human Subject as a living individual about whom an investigator conducting research 1) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or 2) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens. (45 CFR 46.102(e)(1))

> **Intervention**: Includes both physical procedures by which information or biospecimens are gathered and manipulations of the subject or the subject's environment that are performed for research purposes.
>
> **Interaction:** Communication or interpersonal contact between the investigator and the subject.

Private Information: 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 private information: 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).

Identifiable biospecimen: a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

FDA regulations define a Human Subject as an individual who becomes a participant in research, either as a recipient of a test article or as a control (21 CFR 56.102(e) and 21 CFR (812.3(p)). 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. Clinical investigations that use human specimens (e.g., in vitro diagnostic devices, assays, or culture media) involve human subjects.

When the FDA definitions are met, the activity is Research Involving Human Subjects that is FDA regulated. If the HHS definitions are met, the activity is Research Involving Human Subjects that is HHS regulated. If both sets of definitions are met, the activity is Research Involving Human Subjects and is both HHS- and FDA-regulated.

DUHS HRPP Policy

DUHS IRB must review and approve all research involving human subjects before the research begins, and must conduct continuing assessment during the life of the research study, if it meets any of the following criteria:

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

Unless it meets one of the following exceptions:

- The research will be reviewed by an external IRB and an IRB Authorization Agreement is in place
    - When research is reviewed by an external IRB, the DUHS IRB will conduct an administrative review per its policy to ensure compliance with DUHS standards.
- The DUHS IRB determines that:
    - The research meets one or more of the examples of not being engaged in human subjects research listed in OHRP guidance on "Guidance on Engagement of Institutions in Human Subjects Research", dated 10/16/2008 and found at:

https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-engagement-of-institutions/index.html

- The Duke faculty or staff member plans to conduct research with human subjects solely at the Durham Veterans Administration Medical Center (DVAMC), no research funding comes through DUHS, and the investigator has obtained DVAMC IRB approval of that research. (If part of the research is to be conducted within a Duke facility, then the DUHS IRB will review the research)
- The research meets the criteria for exemption from review prior to the initiation of an emergency use of a test article. (see DUHS IRB policy on Expanded Access for an Investigational Medical Product for an Individual Patient, Including for Emergency Use)
- 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.
    - Note that the Privacy Rule (HIPAA), including its research provisions, applies to both living and dead people, and the research provisions apply when the HHS definition of research (45 CFR 46.102(l)) is met.

For further information on resident and trainee requirements when conducting research away from Duke, refer to DUHS IRB "Duke Trainees Engaged in Research Involving Human Subjects at a Site Other Than Within DUHS".

Exemption from IRB Review

A qualified IRB member may determine that an activity does not meet the definition of Research Involving Human Subjects and notify the investigator that the activity does not require further IRB review. The qualifications for conducting such reviews are consistent with those established under DUHS expedited review procedures. They may also determine that research meets the criteria established by HHS and/or FDA for exemption from IRB review including limited review.

Investigators seeking a determination that an activity does not constitute human subjects research or qualifies for exemption from IRB review must submit an "Exemption from IRB" electronic submission through the DUHS IRB system. The submission must include sufficient information to permit the IRB to make the appropriate determination, including a description of the proposed activity, relevant study documents (such as a protocol or study plan when the activity is not fully described within the submission form or when requested by the IRB), and if an exemption is being requested it must also include any participant-facing materials, including recruitment and advertising materials, consent forms, information sheets, scripts, surveys, questionnaires, and other communications or

documentation intended for prospective or enrolled participants, as applicable. Additional materials may be requested by the reviewer to support the determination.

If the reviewer determines that the research does not satisfy the criteria for exemption, the reviewer may not disapprove the research similar to expedited procedures. Instead, the reviewer must provide a rational and require submission of a regular application for review under applicable expedited categories of review, or referral for review by the convened IRB when the research presents greater than minimal risk or otherwise requires convened review.

Any proposed changes to the research activity must be reviewed to determine whether the modifications alter the original determination or subject the activity to additional regulatory or institutional requirements.

As an institutional requirement, all exempt human subjects research is evaluated against DUHS ethical standards, including the criteria associated with limited IRB review where applicable, regardless of whether such review is required under federal regulations. At a minimum the IRB must determine that:

- The research involves no more than minimal risk to participants.
- The selection of participants is equitable and appropriate to the research.
- Adequate provisions are in place to protect the privacy of participants and maintain the confidentiality of identifiable information and identifiable biospecimens, as applicable.
- Additional safeguards are implemented when appropriate to protect the rights and welfare of participants.

If there are interactions with participants in exempt research, the IRB reviewer may determine that a consent process is needed, and that consent process will disclose such information as:

- That the activity involves research.
- A description of the procedures.
- That participation is voluntary.
- Name and contact information for the researcher.
- There are adequate provisions to maintain the privacy interests of participants.

Only the DUHS IRB may make determinations of exemption. Individual Duke researchers are not permitted to make the determination themselves. DUHS adheres to its international research, continuing review, adverse event reporting and suspension, holds and terminations policies for all human subject research including research that's determined to be exempt or require limited review to ensure appropriate review and oversight.

HHS Criteria for Exempt Research

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 considered to be exempt research*(45 CFR 46.104(d) (1)-(6)):*

1. Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
2. Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:
    i. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
    ii. Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
    iii. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).

3. Research involving **benign behavioral interventions** in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the specified criteria (46.104(d)(3)(A-C) is met.

Benign behavioral interventions are:

- Brief in duration.
- Harmless.
- Painless.
- Not physically invasive.
- Not likely to have a significant adverse lasting impact on participants.
- The researcher has no reason to think the participants will find the interventions offensive or embarrassing.
- If the research involves deception of participants regarding the nature or purposes of the research, the participant authorizes the deception through a prospective agreement to participate in research in circumstances in which the individual is informed that they will be unaware of or misled regarding the nature or purposes of the research.

4. Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:
    i. The identifiable private information or identifiable biospecimens are publicly available;
    ii. Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;
    iii. The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b); or
    iv. The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.
5. Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs.
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.

Please note that at this time, exemptions (7) and (8) under 45 CFR 46.104(d) are not applicable for DUHS IRB, as Broad Consent has not been instituted within DUHS. Please also note that exemption (4) is specific to "secondary research". It is the policy of DUHS IRB that research databases that retain identifiers do not meet exemption category (4) and should be submitted as a regular research application.

- The exemptions 45 CFR 46.104(d)(1-6) do not apply to research involving prisoners, as stated in 45 CFR 46 Subpart C except for research aimed at involving a broader subject population that only incidentally includes prisoners.
- The exemptions 45 CFR 46.104(d)(1-5) cannot be applied to FDA regulated research.
- The exemption 45 CFR 46.104(d)(2)(i and ii) may only apply to children if the research involves educational tests or the observation of public behavior when the investigator(s) do not participate in the activities being observed. The exemption 45 CFR 46.104(d)(iii) does not apply to research involving children.
- The exemption 45 CFR 46.104(d)(3) does not apply to research involving children, as stated in 45 CFR 46 Subpart D.

FDA Criteria for *Exemption from IRB Review*

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 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 HHS definition of "research" and involve "human subjects".

Note that 45 CFR 46.104(d)(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).

Institutions Engaged in Research

In general, institutions are considered *engaged* in an HHS-conducted or supported non-exempt human subjects research project (and, therefore, would need to hold or obtain an OHRP-approved FWA and certify IRB review and approval to HHS) when the involvement of their employees or agents in that project includes any of the following:

(1) Institutions that receive an award through a grant, contract, or cooperative agreement directly from HHS for the non-exempt human subjects research (i.e., awardee institutions), even where all activities involving human subjects are carried out by employees or agents of another institution.
(2) Institutions whose employees or agents intervene for research purposes with any human subjects of the research by performing invasive or noninvasive procedures.
(3) Institutions whose employees or agents intervene for research purposes with any human subject of the research by manipulating the environment.
(4) Institutions whose employees or agents interact for research purposes with any human subject of the research.
(5) Institutions whose employees or agents obtain the informed consent of human subjects for the research.
(6) Institutions whose employees or agents **obtain** for research purposes identifiable private information or identifiable biological specimens **from any source** for the research. It is important to note that, in general, institutions whose employees or agents obtain identifiable private information or identifiable specimens for non-exempt human subjects research are considered engaged in the research, even if the institution's employees or agents do not directly interact or intervene with human subjects. In general, obtaining identifiable private information or identifiable specimens includes, but is not limited to:
   (a) observing or recording private behavior;

(b) using, studying, or analyzing for research purposes identifiable private information or identifiable specimens provided by another institution; and
(c) using, studying, or analyzing for research purposes identifiable private information or identifiable specimens already in the possession of the investigators.

For further information, see OHRP guidance on Engagement of Institutions in Human Subjects Research (2008)

Previous Version Date(s): 10/2/2008, 5/19/2011, 7/27/2012, 3/8/2016, 7/26/2021, 11/20/2023