

## Not Human Subjects Research Determination

45CFR46 and 21CFR50 apply to **all research involving human subjects** conducted, supported, or otherwise subject to regulation by any Federal department or agency that takes appropriate administrative action to make the policy applicable to such research. As a result, IRBs must first determine that proposed activities meet the definitions of 'research' and 'human subjects' defined in the regulations.

### Introduction

This document is designed to provide an approach to determining when a proposed activity is human subjects research. Note, if WCM is not engaged in the research, there is no need to approach the human subjects research definition. If WCM is engaged, first, the proposed activity **must** satisfy the definition of 'research.' If the proposed activity meets this definition, and *only* if it meets this definition, IRBs may then approach the human subjects definition.

Often researchers feel that if it involves human subjects it must require IRB review; this is not always the case. If the proposed activity does not satisfy the research definition first, the involvement of humans as participants is irrelevant, even if sensitive information is being collected.

It is important to note that risk is not a deciding factor as to whether a proposed activity is human subjects research nor does a not human subjects research (NHSR) determination mean there is no risk or ethical concern with the proposed activity. An NHSR determination simply means review of the activity is outside of the scope of the IRB. IRBs appropriately excluding themselves from review of NHSR does not preclude an institution from establishing its own policy surrounding the review of protocols that fall outside of IRB purview nor does it preclude ethical conduct.

### Step 1: Research Definition

**Research is a systematic investigation designed to develop or contribute to generalizable knowledge.**

- A **systematic investigation** is an activity that involves a prospective plan that incorporates data collection (qualitative or quantitative) and data analysis to answer a question – this can include testing a hypothesis, establishing clinical practice standards where none previously exists, or establishing a registry or database from which a hypothesis will be tested. Specifically, a systematic investigation involves a local and organized approach to data collection and analysis, developed in advance of project initiation including qualities of:
  - One or more specific questions of interest, often framed as hypotheses, that the project will seek to answer
  - Data collection methods appropriate to address the question(s)
  - Data analysis plans appropriate for the types of data collected
  - An ability to use the analyzed data to answer the questions(s)
- Activities **designed (with intent) to develop or contribute to generalizable knowledge** are those designed to draw general conclusions, inform policy, or generalize findings beyond a single individual or internal program. A study designed to develop or contribute to generalizable knowledge intentionally links to, applies, and/or expands upon existing knowledge. The methods allow for replication and for comparisons with data collected from different samples of the same population, and the results apply to people beyond those directly studied. Qualities include:
  - Basis in theoretical framework of established knowledge
  - Identification of a gap in knowledge that the project plans to address

- Identification and description of one or more specific populations of interest
- Unbiased sampling methods (i.e., random or probability sampling), when feasible, that allow for the recruitment of samples representative of the population(s)
- Operationalization of variables and constructs
- Data collection plans employing measurement tools and techniques with established satisfactory reliability and validity
- Data analysis plans using techniques consistent with those employed in the literature of the theoretical framework and considered appropriate for the type(s) of data collected
- An ability and plan to use the collected and analyzed data to draw meaningful conclusions about the result and link these back to the theoretical framework and identified gap in knowledge

Note, specifically, IRBs must approach the *current* proposed project when thinking about generalizable knowledge rather than future goals for subsequent related research steps. Also, the intent to publish or present findings does not satisfy the criteria for generalizable knowledge. Publication/dissemination is not a determining factor for whether an activity is human subjects research requiring review and approval by the IRB. Results do not have to be published or presented to qualify the activity as research.

In summary, **the proposed project must be a systematic investigation AND designed to develop or contribute to generalizable knowledge, satisfying the qualities described above, to be considered research** according to Federal regulation.

Two questions that will be helpful in determining whether the proposed activity is research are:

1. What do the researchers intend to do in the proposed study? (In other words, what is the true purpose at this stage?)
2. What do the researchers intend to do with the results? (Will they simply improve upon a tool/program/etc. (QA/QI) or are they attempting to validate a tool/program/etc. that has already been developed?)

## Step 2: Human Subjects Definition

**45CFR46 defines a human subject as a living individual *about whom* an investigator (whether professional or student) conducting research:**

- (i) obtains information or biospecimens through intervention or interaction with the individual and uses, studies, or analyzes the information or biospecimens, or
  - (ii) obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.
- **Intervention:** Physical procedures by which data are gathered (e.g., venipuncture) and manipulations of the participant or the participant's environment that are performed for research purposes.
  - **Interaction:** Communication or interpersonal contact between the investigator and participant
  - **Private information:** data about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, or data provided for specific purposes in which the individual can reasonably expect that it will not be made public (such as a medical record)

- **Identifiable:** individual identities can be readily ascertained or associated with the information or biospecimens collected by the investigator

Note, the researcher may be conducting a systematic investigation that involves collecting information **from** people (this includes identifiable data), but it may not be **about** people or human behavior. Also, the standard for identifiability is specifically in the context of accessing data. Anonymous interactions/interventions are still human research.

Two questions that will be helpful in determining whether the proposed activity is about human subjects are:

1. Are data being collected about a “what” or “whom”?
2. Can an individual be linked with his/her/their data points?

## Public Health Surveillance Activities

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\* are deemed **not** to be research per the Revised Common Rule. 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 national or man-made disasters).

*\*A public health authority is defined as an agency or authority of the United States, a state, a territory, a political subdivision of a state or territory, an Indian tribe, or a foreign government, or a person or entity acting under a grant of authority from or contract with such public agency, including the employees or agents of such public agency or its contractors or persons or entities to whom it has granted authority, that is responsible for public health matters as part of its official mandate.*

**For an activity to be deemed a public health surveillance activity, and thus not ‘research,’ it must meet the following three criteria:**

1. The activity must be a public health surveillance activity;
2. The activity must be conducted, supported, requested, ordered, required, or authorized by a public health authority; and
3. The activity must be limited to that 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)

Examples include:

- Safety and injury surveillance activities designed to enable a public health authority to identify, monitor, assess, and investigate potential safety signals for a specific product or class of products.
- Surveillance activities designed to enable a public health authority to:
  - Identify unexpected changes in the incidence or prevalence of a certain disease in a defined geographic region where specific public health concerns have been raised.

- Identify the prevalence or incidence of known risk factors associated with a health problem in the context of a domestic or international public health emergency.
- Locate the range and source of a disease outbreak or to identify cases of a disease outbreak.
- Detect the onset of disease outbreaks or provide timely situational awareness during the course of an event or crisis that threatens the public health, such as a natural or man-made disaster.
- Identify the prevalence or incidence of a condition of public health importance, known risk factors associated with a condition of public health importance, or behaviors or medical practices related to prevalence of a known condition of public health importance (e.g., surveillance of the prevalence of tobacco use, exposure to secondhand smoke, lung cancer, or use of smoking cessation treatments).

## Food and Drug Administration

In addition to the definitions described above, the Food and Drug Administration (FDA) provides the following definitions for research involving human subjects:

- **Clinical investigation (research):** Any experiment that involves a test article and one or more human subjects that is either subject to requirements for prior submission to the FDA under section 505(i), or 520(g) of the act, or is not subject to requirements for prior submission to the FDA under these sections of the act, but the results of which are intended to be 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 are subject to the provision of 21 CFR 58, regarding nonclinical laboratory studies. [21 CFR 50.3(c)]
- **Test article:** Any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354–360F of the Public Health Service Act
- **Human Subject:** 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 human or a patient.

## Department of Defense

In addition to the definitions of ‘research’ and ‘human subject’ per 45CFR46, the Department of Defense (DoD) provides an additional definition for research involving a human being as an experimental subject:

An activity, for research purposes, where there is an intervention or interaction with a living individual for the primary purpose of obtaining data regarding the effect of the intervention or interaction. Research involving a human being as an experimental subject is a subset of research involving human subjects.

Examples of interventions or interactions include, but are not limited to, a physical procedure, a drug, a manipulation of the subject or subject's environment, the withholding of an intervention that would have been undertaken if not for the research purpose. **This definition does not apply to secondary use or observational studies.**

The following activities conducted or supported by the DoD are **not** research involving human subjects:

- Activities carried out solely for purposes of diagnosis, treatment, or prevention of injury and disease in Service members and other mission essential personnel under force health

protection programs of the DoD, including health surveillance pursuant to section 1074f of the Reference (g) and the use of medical products consistent with DoD instruction 6200.02

- Authorized health and medical activities as part of the reasonable practice of medicine or other health professions undertaken for the sole purpose of patient treatment
- Activities performed for the sole purpose of medical quality assurance consistent with 10 USC 1102 and DoDD 6025.13
- Activities performed solely for an Operational Test and Evaluation (OT&E) project where the activities and project meet the definition of OT&E as defined in 10 USC 139(a)(2)(A)
- Activities performed solely for assessing compliance of individuals and organizations with requirements applicable to military, civilian, or contractor personnel or to organizational units, including such activities as occupational drug testing, occupational health and safety reviews, network monitoring, and monitoring for compliance with requirements for protection of classified information
- Activities, including program evaluation, customer satisfaction surveys, user surveys, outcome reviews, and other methods, designed solely to assess the performance of DoD programs where the results of the evaluation are only for the use of Government officials responsible for the operation or oversight of the program being evaluated and are not intended for generalized use beyond such program
- Survey, interview, or surveillance activities and related analyses performed solely for authorized foreign intelligence collection purposes, as authorized by DoDD 5240.01

### Examples of Not Human Subjects Research (NHSR)

The following examples are activities that are generally not considered to be human subjects research because they do not meet the research, human subjects, or both definitions. **Please note, there are always exceptions to the rule, and when unsure, please contact the HRPO Team for assistance.**

#### 1. Program Evaluation/Quality Assurance Review/Quality Improvement Project.

The activity is limited to program evaluation, quality assurance, or quality improvement activities designed specifically to evaluate, assure, or improve performance within a department, classroom, or hospital setting. Specifically, this does not satisfy the definition of “research.”

**Note:** The purpose of a QA study is to assess the quality of a program/product. The purpose of Program Evaluation (PE) is to assess that a program is doing what it is intended to do. Generally QI is designed for the purpose of improving the quality of a service, a program, a process, etc.. A QA, QI or PE study should present no change in risk to participants. These studies are mechanisms to assure that a service, a program, or a process functions optimally. Such projects are usually for internal auditing purposes only.

If you can answer "yes" to all of the following questions, the activity is most likely not human subjects research:

- 1) Will you simply monitor an existing process (this may include evidence-based practice) for which there will be no manipulation of the existing process?
- 2) For QA or PE studies, will physicians or caregivers (parents, teachers, therapists, etc.) provide usual and customary care regardless of the conduct of the study?
- 3) Does the study involve collection of data to which the investigator routinely has access as part of his or her responsibilities within the institution to monitor data associated with, for example: treatment, cost containment, performance, or compliance?

*Note that an evaluation, assurance review, or improvement project designed specifically for a particular setting may yield useful information for similar entities, and may still not satisfy the definition of human subjects research.*

## **2. Case Report**

The project consists of a case report or series which describes an interesting treatment, presentation, or outcome. A critical component is that nothing was done to the patient(s) with prior “research” intent. Additionally, given the small n, generally these studies do not satisfy the definition of research.

*Note that HIPAA or other state or local laws may still apply to this activity. Please refer researchers to the Privacy Office as needed.*

## **3. Course-Related Activity**

The project is limited to one or more course-related activities designed specifically for educational or teaching purposes where data are collected from and about students as part of routine class exercises or assignments and otherwise do not meet the definition of Human Research. Specifically, this does not satisfy the definition of research.

*Note that some course-related activities, even those conducted by students, may yield information suggesting additional investigation or analysis.*

## **4. Journalistic or Documentary Activity (including Oral History)**

The activity is limited to investigations or interviews (structured or open-ended) that focus on specific events (current or historical), views, etc. Such investigations or interviews may be reported or published in any medium, e.g., print newspaper, documentary video, online magazine. Specifically, this does not meet the definition of research.

## **5. Research Using Public or Non-Identifiable Private Information about Living Individuals**

The activity is limited to analyzing data about living individuals (1) where the data have been retrieved by the investigator from public, non-restricted data sets or (2) where the private data have been provided to the investigator without any accompanying information by which the investigator could identify the individuals. Specifically, this does not meet the definition of human subjects.

*Note that “de-identified data” according to HIPAA may be identifiable according to the DHHS definition of “human subjects.”*

## **6. Research Using Health Information from Deceased Individuals**

This activity is limited to analyzing data (identifiable or not) about deceased individuals. Specifically, this does not meet the definition of human subjects.

*Note also that HIPAA or other state or local laws may still apply to this activity. Please refer researchers to the Privacy Office as needed.*

## **7. Instrument/Questionnaire/Tool/Software/Hardware Development**

This activity is limited to interacting with individuals in order to obtain feedback on the types of questions which could or should be used to develop an instrument, tool, software, hardware, or questionnaire. Sometimes, these projects are referred to as ‘human in the loop’ studies, as the researcher simply needs a human to interact with the tool in order to continue development. The focus is on the development and construction of a tool and not on the individuals who are providing the feedback on the questions being developed. This will be true even when the feedback may be specifically sought from an identified group of people most likely to be affected by the topic of the instrument, tool, hardware, software, survey, or questionnaire. The development stage of the project specifically does not satisfy the definition of research.

*Note that once the process gets to the level of testing discriminant, concurrent or predictive validity, or the project goes beyond the scope of development, the activity may need to be reclassified as human subject research.*

**8. Criminal Justice Activities**

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.

**9. Homeland Security/National Security**

Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.

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**Sources:**

1. <https://www.hhs.gov/ohrp/education-and-outreach/online-education/human-research-protection-training/lesson-2-what-is-human-subjects-research/index.html>
2. <https://www.hhs.gov/ohrp/regulations-and-policy/requests-for-comments/draft-guidance-activities-deemed-not-be-research-public-health-surveillance/index.html>
3. <https://www.hhs.gov/sites/default/files/ohrp-what-is-research-and-what-it-is-not.pdf>
4. 45CFR46
5. 21CFR50
6. DoD Instruction 3216.02



## Not Human Subjects Research Determination Checklist

Research		
1. Is the activity a systematic investigation, including research development, testing, and evaluation?	Yes	No
<i>A systematic investigation is an activity that involves a prospective plan that incorporates data collection (quantitative or qualitative) and data analysis to answer a question – this can include testing a hypothesis, establishing clinical practice standards where none previously exists, or establishing a registry or database from which a hypothesis will be tested.</i>		
2. Is the activity designed to develop or contribute to generalizable knowledge?	Yes	No
<i>Activities designed (with intent) to develop or contribute to generalizable knowledge are those designed to draw general conclusions, inform policy, or generalize findings beyond a single individual or an internal program.</i> <i>NOTE: The intent to develop or contribute to generalizable knowledge makes an activity research. Publication/dissemination is not a determining factor for whether an activity is human research requiring review and approval by the IRB. Results do not have to be published or presented to qualify the activity as research.</i>		
<p>If you have answered “no” to any of the above, <b>this is NHSR per the DHHS and no IRB review/approval is required. If FDA may apply, continue with this form.</b></p> <p>If you answered “yes” to both questions or if you are not sure, please <b>continue with this form.</b></p>		
3. Does the project involve a test article subject to FDA regulation, requiring prior submission to the FDA or for which results will be submitted to the FDA as part of a research marketing permit?	Yes	No
<i>A test article is any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354–360F of the Public Health Service Act</i>		
<p>If you have answered “no” to the above, you may <b>end here - this is NHSR per the FDA and no IRB review/approval is required.</b></p> <p>If you answered “yes” or if you are not sure, please <b>continue.</b></p>		

\*Note, if DoD conducted or funded, review NHSR Guidance document for activities that are and are not human subjects research beyond those described in 45CFR46.

Public Health Surveillance		
Is the project a public health surveillance activity?	Yes	No
<i>See Guidance document for definitions. NOTE: Public health surveillance activities are not designed to develop or contribute to generalizable knowledge, but rather to collect information to determine the magnitude of a problem or to improve public health.</i>		
<p>If you answered “yes” to the above question, you may <b>end the form here.</b> This is NHSR and no IRB review/approval is required.</p> <p>If you answered “no” or if you are not sure, please <b>continue.</b></p>		



Human Subjects		
1. Is the information or biospecimen obtained or used for research about living individuals?	Yes	No
<p>If you answered “<b>no</b>” to the above question, you may <b>end the form here</b>. This is NHSR, no IRB review/approval is required.</p> <p>If you answered “<b>yes</b>” or if you are not sure, please <b>continue</b>.</p>		
2. Does the research involve interaction or intervention with humans?	Yes	No
<p><i>Interaction: includes communication or interpersonal contact between the investigator and subject</i>  <i>Intervention: includes both physical procedures by which information or biospecimens are gathered (e.g., venipuncture) and manipulations of the subject or subject's environment that are performed for research purposes</i></p>		
3. Does the research obtain, use, study, analyze, or generate identifiable private information or identifiable biospecimens?	Yes	No
<p><i>Identifiable private information/biospecimen - information/biospecimen for which the identity of the subject is or may be readily ascertained by someone on the research team or associated with the information/biospecimen.</i></p>		
4. Does the research involve human subjects (healthy or patients) who will serve as the recipient of a test article or as a control?	Yes	No
<p><i>A test article is any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354–360F of the Public Health Service Act</i></p>		
<p>If you have answered “<b>no</b>” to all of the above questions, this is NHSR. No IRB review/approval is required.</p> <p>If you answered “<b>yes</b>” to any of the above questions, this activity is human subjects research. If you are unsure, please contact the HRPO Team for guidance.</p>		

\*Note, if DoD conducted or funded, review NHSR Guidance document for activities that are and are not human subjects research beyond those described in 45CFR46.