Penn
University of Pennsylvania
Human Research Protections Program

Is IRB Review Required?

The first question one should consider when assessing the requirement for IRB review is whether the activity meets the regulatory definitions of research with human subjects. Anyone unsure about IRB review requirements and whether their proposed activity constitutes "human research" requiring IRB review should contact the IRB. The IRB staff will determine if the activity is human research. If an activity does not meet the regulatory definitions of research with human subjects, the IRB will issue a determination stating that the project does not require IRB review or approval.

Contents

Defining Human Research

Human Research	Any activity that: • Meets the DHHS definition of "Research" and involves one or more "Human Subjects" as defined by DHHS regulations. OR • Meets the FDA definition of "Research" and involves one or more "Human Subjects" as defined by FDA regulations.

Health and Human Services (DHHS) Definitions

Research	45 CFR 46.102(l) defines research as a *systematic investigation*, including research development, and testing and evaluation, *designed to develop or contribute to generalizable knowledge*.
Human Subject	45 CFR 102(e)(1) defines a human subject as a living* individual about whom an investigator conducting research: • Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; OR • Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens. **Intervention:** • Physical procedures by which information or biospecimens are gathered (e.g., venipuncture); • Manipulations of the subject or the subject's environment that are performed for research purposes. **Interaction:** Communication or interpersonal contact between investigator and 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* that has been provided for specific purposes by an individual and *that the individual can reasonably expect will not be made public* (e.g., a medical record). **Identifiable† private information:** Private information for which 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 **Note*: The HIPAA Privacy Rule requires that a deceased individual's PHI remain protected for 50 years following the date of the person's death. Hence, even if the DHHS human subject definition is not met, HIPAA compliance may still be required and a privacy review by the IRB may still be required.

	†*Note*: Coded information and biospecimens are considered to be identifiable. Coded means the information or biospecimen is assigned a unique random identifier that is separately linked to subject identifiers. Re-identification is possible.

Food and Drug Administration (FDA) Definitions

Research (Clinical Investigation)	FDA regulations at 21 CFR 50.3(c), 21 CFR 56.102(c), 21 CFR 312.3(b), and 21 CFR 812.3(h) define a clinical investigation to be: • any study in which a test article (i.e., drug) is administered, dispensed to, or used, involving one or more human subjects. OR • Research involving "one or more subjects to determine the safety and/or effectiveness of a device." Clinical Investigations are considered to be "FDA regulated" research regardless of whether the study requires an IND or IDE, or the study is exempt from IND or IDE regulations.
Human Subject	21 CFR 50.3(e): An individual who is or becomes a participant in research, either as a recipient of a drug or device, or as a control. 21 CFR 812.3(p): An individual on whose specimen a medical device is used.
Device	A device could be any of the following: instrument, apparatus, implement, machine, contrivance, implant, in-vitro diagnostic, lab developed test, in vitro reagent, assay, software application, algorithm, or other similar or related article or component, part, or accessory.
Drug	A drug could be any of the following FDA: • Prescription or over-the-counter drug • Biologic • Placebo • Vitamin, Mineral, Dietary Supplement or other GRAS product • Food / Food Additive • Cosmetic

Activities that are Not Human Subjects Research as outlined by DHHS

Scholarly and Journalistic Activities

These activities include oral history (in which an individual conducts a series of taped interviews with participants in a particular historical event or period), 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.

Public Health Surveillance Activities

Public Health Surveillance activities consist of the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized **by a public health authority.** These activities do not qualify as research.

However, 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).

Activities Authorized by Law or Court Order for Criminal Justice or Criminal Investigative Purposes

Collection and analysis of information, biospecimens, or records by or for a criminal justice agency are not considered to be research when the activities are authorized by law or court order solely for criminal justice or criminal investigative purposes.

Activities in the Gray Zone (may or may not meet the definitions of human research)

Medical Case Reports

For IRB purposes, a single case report is a retrospective analysis of one, two, or three clinical cases.

A single retrospective case report is a medical/educational activity and does not meet the Federal Policy for the Protection of Human Subjects definition of "research" which is “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.”

Therefore the activity does not require review by the IRB. Per institutional policy, the review of medical records for publication of "case reports" of typically three or fewer patients is NOT considered human research and does NOT typically require IRB review and approval because case reporting on a small series of patients does not involve the formulation of a research hypothesis that is subsequently investigated prospectively and systematically for publication or presentation. Reporting or publication is not typically

envisioned when one interacts clinically with the subject. *Likewise, while it is best practice to obtain informed consent from the patient(s), the IRB does not require this.*

Under HIPAA, a single case report is an activity to develop information to be shared for medical/educational purposes. Therefore, the use of protected health information to prepare a paper for publication of a single case report does not require IRB review for HIPAA purposes. **If, however, the investigator wishes to publish data with HIPAA identifiers, the patient must provide HIPAA authorization.**

When larger series of patients are being reported, investigators usually begin to ask specific research questions and formal systematic collection of data occurs, moving these activities closer to prospectively designed research. Researchers are advised to consult with the IRB when uncertainty exists about whether the activity meets the definition of human research.

It should also be noted that teaching and soliciting colleagues' advice on clinical care of a specific patient or groups of patients during presentation of a case at departmental conferences DOES NOT require IRB review. Generalized commentary by a clinician on the outcome of their clinical care of patients in accepted venues for discussion of clinical management is also not considered research requiring IRB review, if there is no prospective research plan, and no formal, systematic and prospective collection of information. This type of communication may occur at hospital or practice meetings, in continuing education venues, or in editorials, where the comments are explicitly identified as personal experience and not formal clinical research.

<u>Research with Existing Private Data or Specimens</u>
Some research with existing de-identified OR unlinked, coded private information or biological specimens does not qualify has human subjects' research.

- *Existing* means that the data or specimens were not collected for the currently proposed projects.
- When HIPAA applies, *de-identified* means the data or specimens may not contain any HIPAA identifiers, including indirect identifiers such as elements of dates and zip codes.

Examples: Receipt of de-identified data or specimens that were previously collected as part of a research study by another investigator; Receipt of de-identified data or specimens from a data or specimen registry; Receipt of de-identified data from a registry where the data can be directly downloaded from the data holder's website.

In the case of coded data, the investigator must not be able to link the coded data/specimens back to individual subjects at any point during the research. If the provider of the data/specimens has access to the identity of the subjects (e.g. subjects' names, MRN, etc.), the investigator must enter into an agreement with the data/specimen provider that states under no circumstances will the identity of the subjects be released to the investigator.

Chart Reviews
Chart reviews typically qualify as human subjects' research requiring review under exempt category 4 as identifiers usually need to be accessed or collected even for a short period to connect data from multiple sources. Likewise, HIPAA regulations apply and a privacy board review by the IRB is needed.

In Vitro Device Studies
Unlike DHHS regulations, *FDA regulations do not provide for exemption from IRB review when research involves existing specimens and the investigator records information without identifiers or linking codes*. Nor do FDA regulations define "human subjects" with reference to the identifiability of the subject or of the subject's private information (i.e., the donors of specimens/samples remain "human subjects" even when the specimens/samples are de-identified).

Current FDA guidance indicates that IRB review is required for any study involving human specimens where the specimens are used to determine the safety and/or effectiveness of a device, even when the research involves no identifiers and the biological materials cannot be linked to any identifying information. *These studies are considered to be clinical investigations (i.e., research), and do not qualify for exempt level review*. Likewise, ***FDA guidance dictates informed consent must be obtained when the specimens are identifiable (page 5).***

Note: Given the complexities above, investigators are not allowed to determine that research with existing private data or specimens is not human subjects research. A request for verification should be submitted to through eIRB.

Student Projects
Generally, student research involving human subjects falls into one of two categories:

1. Directed or independent Research Projects (e.g., honors or graduate theses): Employ systematic data collection with the intent to contribute to generalizable knowledge
   - Require IRB prospective IRB review and approval.

2. Research Practica: A course of study that involves the supervised practical application of previously studied theories of research method. The goal is to provide research training.
   - Does not require IRB review.

   Frequently, schools offer courses that require students to undertake projects in which other people are interviewed, observed, or otherwise serve as participants. The purpose of these course projects is to train students and provide them with a closer

view of social, educational, or psychological processes, and an opportunity to practice various research methods.

Provided such projects are ***not designed to develop or contribute to generalizable knowledge****, these projects are* ***not considered to be research*****,** and thus, IRB review and approval are not required. For example:

- If a project involves the replication of an experiment with known results, then the project is not designed to develop or contribute to generalizable knowledge and the project is not research.
- If a project involves students using research methods (e.g., interview techniques or survey techniques), the results of those methods will be used to evaluate the students' ability to apply these techniques, and the results will not be used to test a hypothesis, then the project is not designed to develop or contribute to generalizable knowledge and the project is not research.

Research pratica that involve the testing or confirmation of a hypothesis may be research. If the project involves the collection of private identifiable data about living individuals or the collection of data about living individuals through interaction or intervention with those individuals, then before implementation the activity should be brought to the IRB for a determination of whether the activity is human research and requires IRB review.

Other Activities that are Not Human Subjects Research

Activities that fit any of the categories below typically do not need IRB review.

1. **Internal departmental, school, or other University data collection** for administrative purposes.

   Examples: teaching evaluations; customer service surveys; service surveys issued or completed by University personnel for the intent and purposes of improving services and programs of the University or for developing new services or programs for students, employees, or alumni, *as long as the privacy of the subjects is protected, the confidentiality of individual responses are maintained, and survey participation is voluntary*. This would include surveys by professional societies or University consortia.

   Note: If at a future date, an opportunity arose to contribute previously collected identifiable or coded survey data to a new study producing generalizable knowledge, IRB review may be required before the data could be released to the new project.

2. **Information-gathering on processes, services, or policies** without gathering information about living individuals.

   Examples: surveying pet adopters about their pet's behavior; canvassing librarians about inter-library loan policies or rising journal costs; asking teacher what methods are in use at their schools or asking for aggregate information about their classes

(e.g., class size or composition); asking emergency room physicians what procedures are used for treating a particular disease.

3. **Innovative clinical practice that does not involve investigational test articles** (drugs or devices not approved by FDA), except when it meets the definition of "research" above. An innovative clinical practice is an intervention or therapy designed solely to enhance the wellbeing of an *individual* patient or client. The purpose of an innovative clinical practice is to provide diagnosis, preventative treatment, or therapy to a particular individual. Note: When innovative clinical practice differs significantly from routine practice, it should be viewed and treated as such with appropriate safeguards in place to protect the rights and welfare of the patients.

4. **Quality improvement projects**, except where they meet the DHHS or FDA definitions of research outlined above. **Please review the QI / PI guidance.** Any individual who is unsure whether or not a proposed quality improvement project should be classified as research should submit a quality improvement application for review.

5. **Research where Penn is not engaged in human subjects' research**. Examples: Penn faculty or staff act as consultants on research but, at no time, obtain, receive, or possess identifiable private information or specimens; Penn faculty or staff perform commercial services for other investigators; Penn faculty or staff inform prospective subjects about the availability of research but are not involved in consenting, research interactions, nor interventions.

   Note: the examples above are not an all-inclusive listing. Please refer to the DHHS Engagement in Research Guidance for a full detailed list.

6. **Research involving cadavers, autopsy material or biospecimens from deceased individuals.** While research with cadavers and autopsy materials does not meet the federal regulatory definitions of human research, the School of Medicine policies require submission to the Morgue of research proposals involving cadavers or recognizable body parts.

   Note: Collection of PHI from deceased patients requires HIPAA compliance and a privacy review by the IRB may still be required.

Not Human Research Determinations by the IRB

Investigators are encouraged to use the Human Subjects Research Determination Form to guide the decision about whether an activity constitutes human research under DHHS or FDA regulations. If a determination is required by a funding agency or sponsor, investigators may submit a request for written confirmation and the Human Subjects Research Determination Form to the IRB and the IRB will provide a written

response. IRB staff are available by telephone or email to provide guidance as to whether a project is human research as defined above.

References

- US HHS Office of Human Research Protections (OHRP) Decision chart to assist in determining whether a project is human research. Chart 1: Is an Activity Research Involving Human Subjects? https://www.hhs.gov/ohrp/regulations-and-policy/decision-charts-2018/index.html#c1

- Food and Drug Administration Guidance on Informed Consent for In Vitro Device Studies using Specimens that are not Individually Identifiable: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-informed-consent-vitro-diagnostic-device-studies-using-leftover-human-specimens-are-not

- OHRP Guidance on Research Involving Coded Private Information or Biological Specimens https://www.hhs.gov/ohrp/coded-private-information-or-biospecimens-used-research.html

- OHRP Quality Improvement Activities: Frequently Asked Questions https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/quality-improvement-activities/index.html

- OHRP Guidance: Engagement in Research https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-engagement-of-institutions/index.html

- Federal Policy for the Protection of Human Subjects (Common Rule) https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/revised-common-rule-regulatory-text/index.html

- The Belmont Report https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html

- Pritchard, Ivor A. Searching for “Research Involving Human Subjects”: What is Examined? What is Exempt? What is Exasperating; IRB: Ethics and Human Research 23, no.3 (2001), 5-12