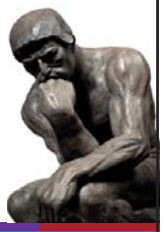
Key Decision Points: Is it Research Involving Human Subjects? Is it Exempt? Is IRB Review Required?



PRIM&R
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

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Welcome!

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Objectives

- To review regulatory criteria for making determinations that a proposed activity is
  - Not human subjects research
  - Exempt
  - Eligible for expedited review
- To discuss the positive reasons for applying these criteria appropriately… and the negative consequences of over-applying IRB review

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Mindset is Important Starting Point

- There is one way to guarantee no risk of harm to subjects → do no research
  - But this also carries risk and ignores the societal good
- Institutions, IRBs, and people working in them have a conscious choice where they fall along a philosophical/aspirational spectrum

Protect at all costs Perfection Risk averse	?	Facilitate research Reasonable person standard Risk tolerant

Beware of the Worst-Case Scenario

In the absence of demonstrable harms

- Consistently over-extending the regs, or protecting against hypothetical worst- case scenarios that have never occurred…
  - Protects very little
  - May actually harm

Rhetorical Questions… Or are they?

- If a little protection is good, shouldn't a lot of protection be better?
  - Not necessarily!
- What is the harm in erring on the side of reviewing things that might technically fall outside those (admittedly blurry) lines?
  - Potentially a lot!

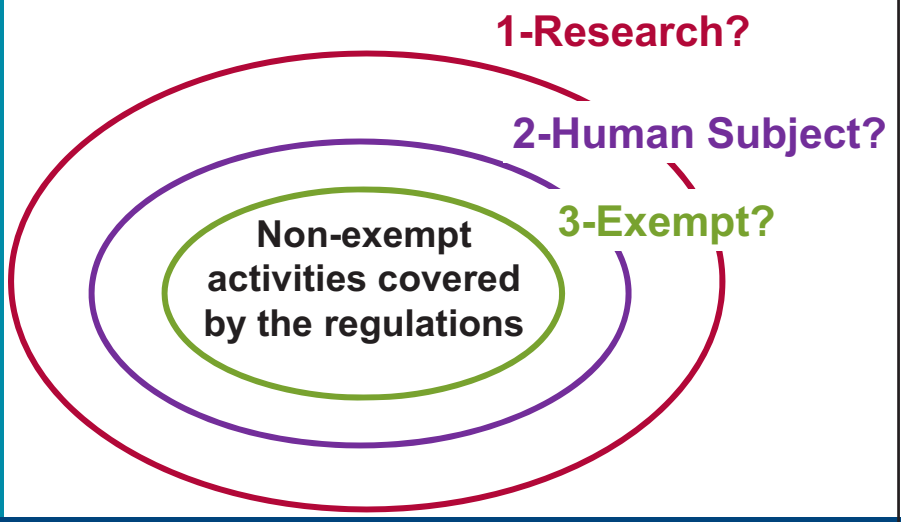
Negative Consequences to Well-Intended Actions

- There are problems with over-extending regulatory oversight to activities that don't require it
  - None of us has unlimited resources
    - Time, staff, IRB members, budgets
    - Where are you going to spend yours?
  - Creates ill will and erodes credibility with researchers… which you may want later
  - IRBs don't do well with "things" that aren't human subjects research and don't fit with the protective mechanisms at our disposal
  - Promotes mission creep

Don't Jump Ahead

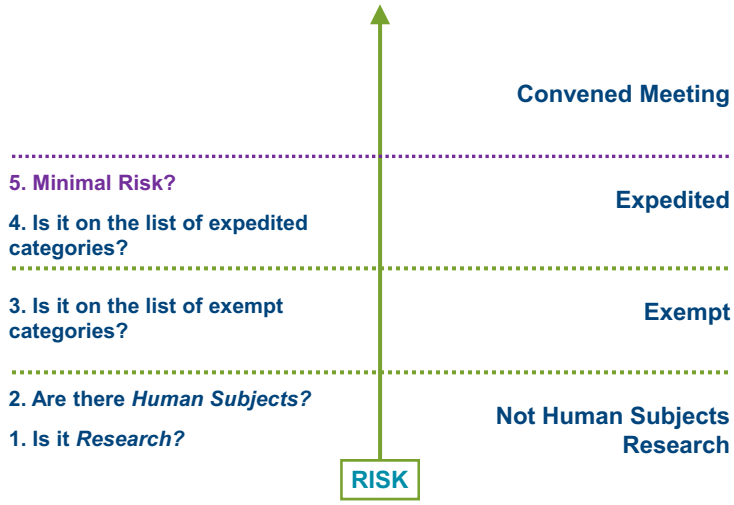
- Applying the definitions and decision points IN ORDER is key to making this work
- Jumping ahead in the order or skipping steps creates an illogical mess
  - e.g., applying regulatory requirements for consent to activity that is not research involving human subjects

Drawing the Lines with Key Definitions



Adapted from OHRP

And for those who are "linear" rather than "circular" thinkers…



Little words can have big impact when applying the regulations…

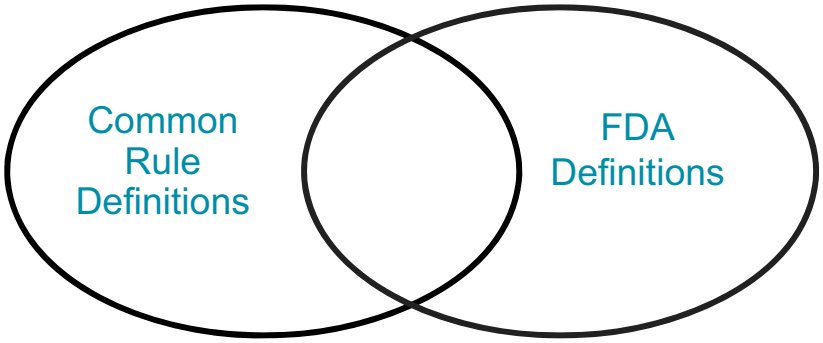
"…and…"

"…if…"

"…or…"

"…unless…"

There are Two Definitions of Human Research



- The difference matters
- Decide systematically

HHS (Common Rule) Definition of *Human Subjects Research*

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Line 1: Definition of Research

A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

45 CFR 46.102(d)

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"Research" – How do you decide?

- Are the activities systematic?
  - Is there a protocol or plan?
- What is the intent?
  - Would the same thing(s) be done if there was no professional recognition attached?
  - Note that intent to publish may not be a reliable indicator
- Will activities contribute to "generalizable knowledge?"
  - Inside or outside the institution?

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Quality Improvement Project

- Are procedures systematic?
- What is the intent?
- Will the findings be used to contribute to generalizable knowledge?

Line 2: Definition of Human Subject

A living individual about whom an investigator conducting research obtains:

(1) Data through intervention or interaction with the individual; or

(2) Identifiable private information.

45 CFR 46.102(f)

"…about whom…"

- The two most misunderstood or misapplied words in the Common Rule?
- It does not say "…FROM whom…"
- Two people talking to each other does not (automatically) a human subject make
  - See above, re: jumping ahead

Do the activities involve intervention or interaction?

- Intervention: 1) Physical procedures by which data are gathered, and 2) Manipulations of subject or subject's environment for research
- Interaction: Communication or interpersonal contact between researchers and subject
- *If Yes → Does not matter whether there are identifiers, activities involve human subjects*

Private + Identifiable

Private information must be individually identifiable in order for obtaining the information to constitute research involving human subjects.

45 CFR 46.102(f)

Is the information private AND identifiable?

- Private?
  - Behavior in context where individual can reasonably expect no observation or recording
  - Provided for purposes that individual can reasonably expect will not be made public (e.g., medical records)
- Individually identifiable?
  - Can the researchers "readily ascertain" the subject's identity?
  - Are data coded or de-identified?

OHRP Guidance on Research Involving Coded Private Information or Biological Specimens

OHRP does not consider research involving only coded private information or specimens to involve *human subjects* if the following conditions are both met:

(1) The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and

(2) The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example, there are agreements, procedures, or legal requirements in place that prohibit the release of the key to the code to the investigators under any circumstances until the individuals are deceased.

Case Studies: Ground Rules

- Brief case studies will be used to illustrate decision points
- The information presented in the cases is not meant to be complete or detailed
- Cases are based on real scenarios
- Webinar participants will be asked to select best response (same five options for each)
- Faculty will share their views, but there may be no “right or wrong”

Case Study #1

A faculty member helps a colleague at another institution develop a survey given to the colleague's students. Students are asked for feedback on the course content, assignments, and tests. (Providing names on the survey is optional.) The faculty member will also help to analyze the survey results; names (if any) will not be removed before surveys are sent to the faculty member. Results will be used primarily to improve the course, but may be published in the future. If published, the faculty member would be named as an author.

POLLING SLIDE

The activity described in the case is:

A. NOT human subjects research

B. EXEMPT human subjects research

C. Human subjects research that is eligible for EXPEDITED review

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E. Human subjects research that requires IRB review, but my institution is NOT ENGAGED

Case Study #2

A researcher wants to review internet sites with chat rooms and an “Ask the Experts” feature. She will review sites commonly used by the diabetes community and other common disease communities. The researcher will visit 35 sites and review the “Ask the Experts” posts. When a person asks a question, she will record how long it takes to answer and rate the quality of the response based on a set of criteria established by the medical community for that disease’s management. The results will be published.

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FDA Definition of Human Subjects Research

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FDA research? Why you should care…

- More than research involving INDs/IDEs
- FDA regulations apply to most research activities involving drugs or medical devices (approved or investigational)
- May also include data submitted to FDA
- It is important to be able to recognize FDA-regulated research → requirements differ

FDA Definition of "Research"

- **Clinical Investigation**: Any experiment involving a test article and one or more human subjects that either
  - Must meet the requirements for prior submission to FDA
  - The results of which are intended to be submitted to or held for inspection by FDA as part of an application for a research or marketing permit
- **Research, clinical research, clinical study, study, clinical investigation**

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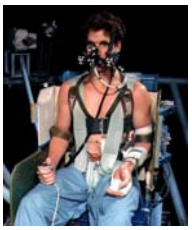
What is an experiment?

- **Experiment**: Any use of a drug except for the use of a marketed drug in the course of medical practice

21 CFR §312.3(b)

- **Experiment**: Any use of a device to evaluate its safety or effectiveness



21 CFR §812.2(a)

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FDA Definition of "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 individual (human) or a patient.

21 CFR §50.3(g)
21 CFR §56.102(e)

FDA Definition of "Human Subject"

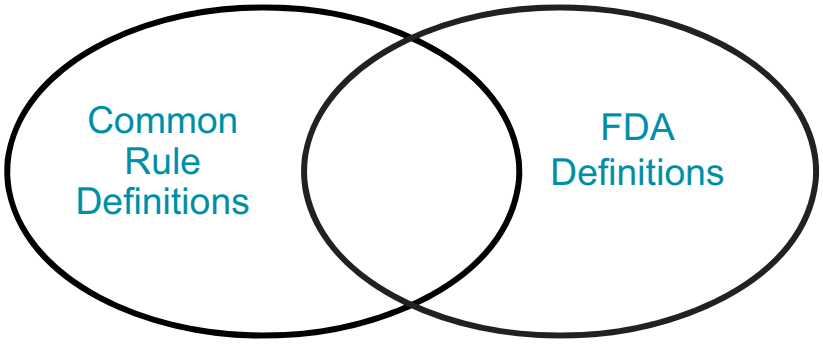
- A human (in normal health or with a medical condition or disease) who participates in an investigation, on whom *or on whose specimen* an investigational device is used, or as a control.

21 CFR §812.3(p)

Summary of FDA Definition(s) for "Human Subject"

- Individual who receives a test article
- Individual who serves as a control
- For medical device research this includes human specimens
- Subjects may be healthy or have a medical condition or disease

There are Two Definitions of Human Research



- The difference matters
- Decide systematically

Case #3

Dr. Bambino is concerned about the efficiency, drug utilization, and quality of care in the neonatal intensive care unit. She is particularly interested in the use of an expensive treatment regimen. She conducted a 3-month study involving the unit's physicians, nurses, and staff, as well as the medical records of premature babies. Upon completion of the study, Dr. Bambino used the data to make improvements in the unit. She then presented the data during pediatric grand rounds.

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Applying the Exemption Categories to Human Subjects Research

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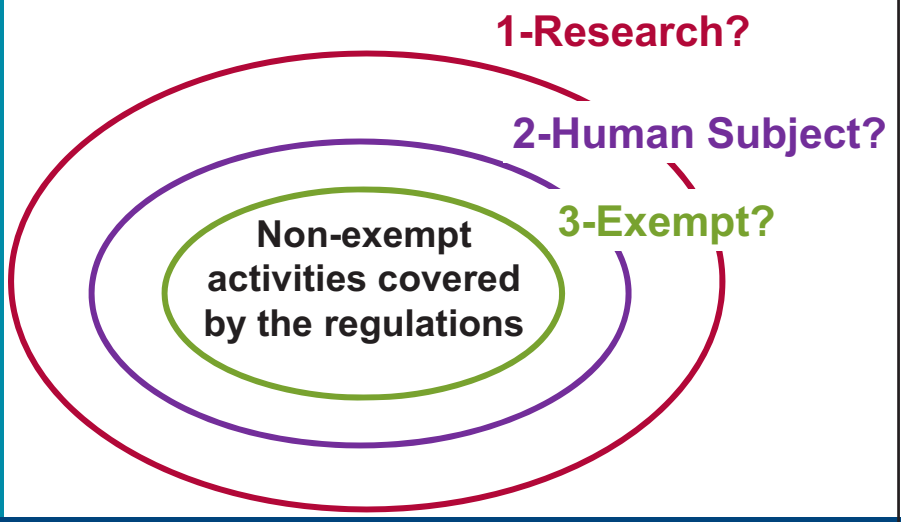
Line 3: Consider the Exemptions



Adapted from OHRP

General Guidance

- Who determines that a research study is exempt?
  - IRB is not required to make this determination. This is a matter of institutional policy.
- What about risk assessment?
  - Regulations are silent on risk, but many institutions presume that exemptions are limited to research involving "no greater than minimal risk."
- Can research with "vulnerable populations" be exempt?
  - Allowed with pregnant women (Subpart B), not with prisoners (Subpart C), and mostly allowed with children (Subpart D)

45 CFR 46.101(b)

- *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.*
  - Key phrases:
    - "…the only involvement…"
    - "…one or more…"
    - "…this policy…" → 45 CFR 46, Subpart A → Common Rule → all the stuff that IRBs do!

45 CFR 46.101(b)(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.

Tips in Applying Category 1

- What is an "established or commonly accepted educational setting"?
  - Can include nontraditional settings, so long as established in the local area
    - Grocery store (e.g., nutrition class)
    - Pharmacy
    - Automotive garage (e.g., safe driving or how to do preventative maintenance on a car)
- What are "normal educational practices"?
  - Also not restricted to traditional settings, so long as established in the setting
    - Computerized training
    - Use of a kiosk to provide education

45 CFR 46.101(b)(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 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.

Category 2 Tips: Beware the Overly Restrictive Interpretation

- Category 2 does not require "anonymous" surveys
  - Information must be both identifiable **AND** potentially damaging before this exemption is disallowed
- Many (most?) survey and interview studies may be eligible for exemption

What is "observation of public behavior"?

- OHRP considers "public behavior" to be that generally open to view by any member of a community and/or which would not involve any special permission to observe → at a park, movie theater, mall, etc.
- What occurs in a classroom would not generally be considered observation of public behavior.

Category 2: Limited When Children are Involved

- 5 of 6 exemptions apply equally to research with children and adults. Category 2 is narrowed in scope by Subpart D.
- Where children are involved, use of survey or interview procedures is eliminated from this exemption.
- Exemption may still apply if the only activities involving children are educational tests or observation of public behavior, where the **investigators do not participate** in the activity being observed.

45 CFR 46.101(b)(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.

45 CFR 46.101(b)(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.

What does "existing" mean?

- "Existing data, documents, records, pathological specimens, or diagnostic specimens" means existing at the time the research is proposed
  - Retrospective chart reviews = exempt
- Research using materials created after the research is proposed would not be exempt
  - Prospective chart reviews ≠ exempt

What is "publicly available?"

- Publicly available means data are available to anyone
  - Data sets that have restricted access are not publicly available
- Are Facebook or internet chat rooms publicly available sources of data?

OHRP on Information Recorded by Investigators

- Category 4 permits recording of identifiable information for sole purpose of linking to other records of interest
  - e.g., to identify which medical charts to pull
- Once records of interest have been identified, no identifying information may be recorded for research analyses

45 CFR 46.101(b)(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.

Public Benefit and Service Programs

- Program must deliver a public benefit (e.g., Medicare or Social Security Act)
- Pursuant to specific federal statutory authority
- Not for state or local projects → limited to projects conducted by or subject to approval of federal agencies, and should not be invoked without authorization or concurrence by the funding agency

45 CFR 46.101(b)(6)

- Taste and food quality evaluation and consumer acceptance studies, if
  - i. Wholesome foods without additives are consumed
  - ii. 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.

So, if a study is exempt, does that mean a PI can do ANYTHING he/she wants??

- No. It just means that risk is low enough that applying regulatory requirements may be overkill
- Even though a study may be exempt…
  - It is still HSR
  - Basic principles still apply
    - For example, respect for persons and common courtesy suggest we still get consent for research involving direct interaction, even if not required by the regs
- Same logic can be applied to other "requirements" under your SOPs

Case Study #4

For his Master's thesis, a social work student would like to study utilization of services in a local homeless shelter. The student will volunteer at the shelter for 3 months so that he can interact directly with individuals who receive services there. The student will inform everyone who comes into the shelter that he is conducting research. He would like to interview individuals at the shelter to determine how many during the last year also received free medical care or were hospitalized during this time. No names will be collected.

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Case Study #5

A medical resident is required to complete a research project as part of her internal medicine rotation. She has heard that the epidemiology department already collected data on patients who were hospitalized in the recent flu outbreak. The resident plans to analyze these data and review the patients' medical records to look for pre-existing conditions or other factors the patients may have had in common. She will record data without identifiers and plans to present her findings at the residency conference, held each spring at a nearby hospital.

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Case Study #6

A pharmacology student wants to compare the treatment outcomes of two drugs used to treat arthritis. He will obtain coded health information of patients treated with Drug A or Drug B from the clinic where they were treated. The data will include only patient age, gender, diagnosis, treatment, and health status at the end of 6 months of treatment. The student and clinic director sign an agreement prohibiting the release of the key to decipher the code under any circumstances, until after the individuals are deceased.

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Expedited Review

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Expedited Review

- Performed by Chair or one or more experienced members
  - Outside of convened meeting
- Can be used for initial review, continuing review, and for minor changes
- Reviewers may not disapprove research
- Same regulatory criteria for approval

Criteria for Approval of Research

45 CFR 46.111 and 21 CFR 56.111

- Risks are minimized
- Favorable risk-potential benefit analysis
- Equitable subject selection
- Informed consent sought
- Informed consent documented
- Data will be monitored for safety
- Privacy is protected; confidentiality maintained
- Safeguards for vulnerable individuals

Expedited Review

- Categories 1-7 apply to initial review
- Categories 8, 9 for continuing review
- Activity must be in category on the list
- Research must be minimal risk
  - Should not be considered minimal risk just because activity is on the list

Expedited Review Categories 1-2

1. Clinical studies of drugs and medical devices when:
   a) An IND is not required
   b) An IDE is not required, or the medical device is approved for marketing and used in accordance with its labeling.
2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture from:
   a) Healthy, non-pregnant adults who weigh at least 110 lbs, ≤ 550ml/ 8 weeks and not more than twice/week
   b) Adults and children, ≤ the lesser of 50ml or 3ml/kg in 8 weeks; collection not more than twice/week.

Expedited Review Category 3

3. Prospective collection of biological specimens by non-invasive means:

   Examples: (a) hair and nail clippings (b) deciduous teeth at exfoliation or extraction (c) permanent teeth if a need for extraction (d) excreta and external secretions (e) uncannulated saliva collected in unstimulated fashion or by chewing gumbase or wax, or by applying a dilute citric solution (f) placenta removed at delivery (g) amniotic fluid obtained at time of membrane rupture (h) supra- and subgingival dental plaque and calculus, if collection not more invasive than routine teeth scaling by accepted techniques (i) mucosal and skin cells collected by buccal scraping, skin swab, or mouth washings (j) sputum collected after saline mist nebulization.

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Expedited Review Category 4

4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves:

   Examples: (a) physical sensors applied to body surface or at a distance, not involving significant energy or an invasion of the participant's privacy (b) weighing or testing sensory acuity (c) magnetic resonance imaging (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing.

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Expedited Review Categories 5-7

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes.
6. Collection of data from voice, video, digital, or image recordings made for research purposes.
7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

Expedited Review Category 8

8. Continuing review of research previously approved by the convened IRB under any of the following conditions:
   a) Where (i) the research is permanently closed to enrollment of new participants (ii) all participants have completed all research-related interventions, and (iii) the research remains active only for long-term follow-up of participants
   b) Where no participants have been enrolled and no additional risks have been identified
   c) Where the remaining research activities are limited to data analysis.

Expedited Review Category 9

9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption, where categories 2 through 8 do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

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Engagement of Institutions in Human Subjects Research

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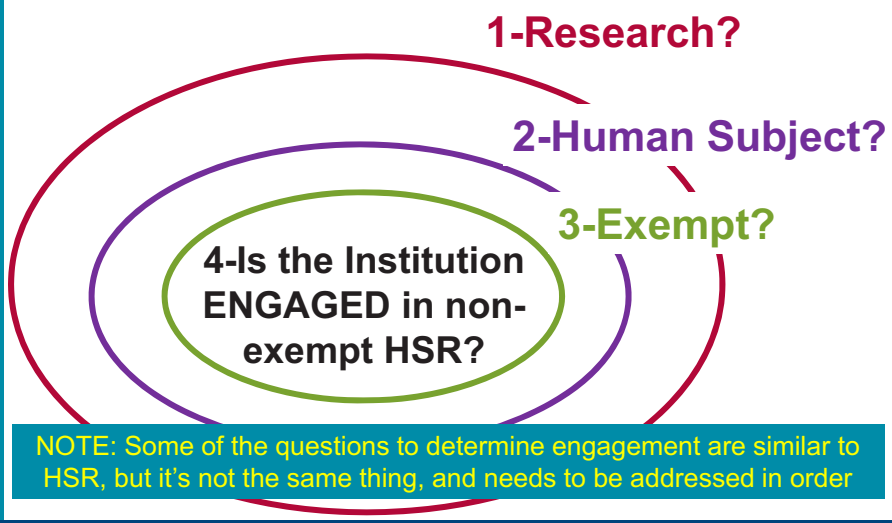
Line 4: Engagement



NOTE: Some of the questions to determine engagement are similar to HSR, but it's not the same thing, and needs to be addressed in order

Adapted from OHRP

Revisiting Case Study #1

A faculty member helps a colleague at another institution develop a survey given to the colleague's students. Students are asked for feedback on the course content, assignments, and tests. (Providing names on the survey is optional.) The faculty member will also help to analyze the survey results; names (if any) will not be removed before surveys are sent to the faculty member. Results will be used primarily to improve the course, but may be published in the future. If published, the faculty member will be named as an author.

Revisiting Case Study #1

This activity is still not research involving human subjects.

HOWEVER, the faculty member might appear to be ENGAGED if her activities are considered in the wrong order, without first determining if her colleague at the other institution is conducting human subjects research!

Case Study #7

A researcher will invite minority adolescents to participate in after-school workshops. He will use a pre-test to gather background data and measure attitudes toward math, followed by unique math instruction (involving computer software tools) that integrates relevant material from their own cultures, followed by a post-test. Results will be used to determine not only the effectiveness of the tools being evaluated, but also whether the pre-test played a role in guiding/changing the students' attitudes about math.

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Case Study #8

A physician wants to compare the treatment outcomes associated with two drugs used to treat arthritis. He will obtain the individually identifiable health information of patients treated with either Drug X or Drug Y by reviewing patients' medical records at the clinic where the patients are treated. The physician will record only patient age, gender, diagnosis, treatment, and health status at the end of 6 months of treatment. The physician will code the records to maintain confidentiality, and to allow him to collect 1-year follow-up data.

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Case Study #9

Dr. A. Orta, a cardiac surgeon, wants to conduct research using 25 leftover tissue specimens from routine biopsies he will obtain during open heart surgeries on his patients over the next 2 months. No additional information from medical records is needed for the planned analysis.

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Case Study #10

Researchers want to contact patients who were treated for pneumonia with an FDA-approved drug, asking them to complete a short survey and undergo a chest x-ray at their next clinic visit. The researchers will also obtain the patients' age, height, weight, adverse effects, and overall health status from their medical records. The information will be recorded so that they cannot link the data back to an individual patient.

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Questions and comments

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Amy Davis, JD, MPH
Senior Director for
Programs and Publications

Please complete the evaluation.

Thank you!

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