Determining Whether Your Project Might Require an Exemption or IRB Review

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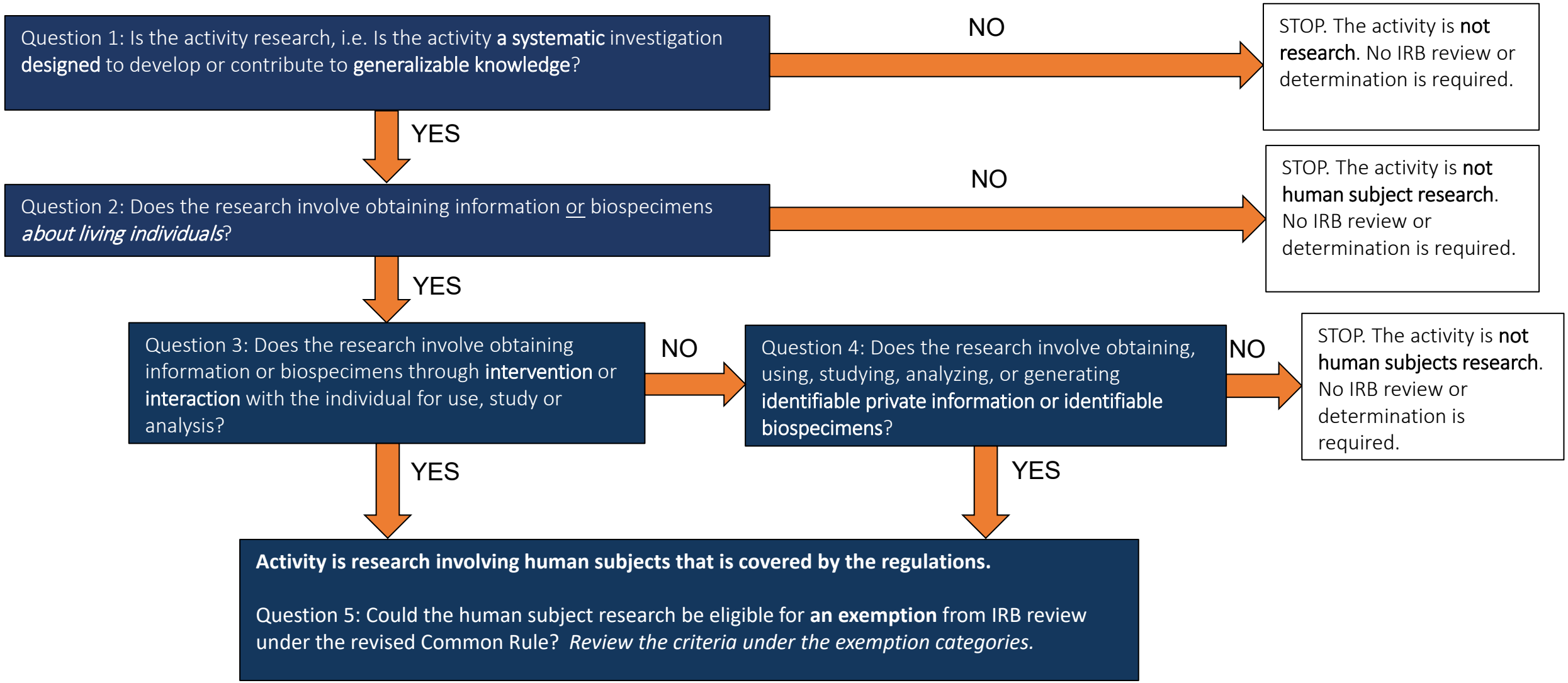
Background

- Subpart A ("the Common Rule") of the DHHS Regulations for the Protection of Human Subjects Research (45 CFR 46) was revised and required compliance as of January 21, 2019. It is referred to as the 2018 Common Rule (a.k.a. the "Revised Common Rule").
- OHSRP policy was revised as of January 21, 2019 to remove the mandatory requirement to submit for a determination of "not human subjects research". For more information, see "Does Your Project Require Submission for a Determination of NHSR or IRB Exemption".

Is The Activity Research Involving Human Subjects?



Question #1: “Research”

- OHSRP is commonly asked whether a certain activity requires IRB review or an exemption.
- Question #1: Is the activity research, i.e., a **systematic** investigation, including research development, testing and evaluation, **designed** to develop or contribute to **generalizable** knowledge? (45 CFR 46.102(l))
  - Definition of **systematic**: done or acted according to a fixed plan or system; methodical in procedure or plan
    - Does the project include a research objective or a hypothesis?
    - Is the purpose of the project to contribute to **generalizable knowledge** about certain class or category of subjects in the U.S. or world?

Generalizable Knowledge

- Does the **design** allow the results to be **generalized** to a population beyond just those who were included in the project?

- If **yes**, to all of the above, the project might meet the definition of **research**.

“Research” vs. “Not Research”

- What is the question you are trying to answer?
  - Is a **tool, system, procedure or process**, etc. **effective in meeting a certain desired outcome**? = **research**
  - What is the best way to **implement** a tool, system, procedure or process, etc. that has already proven to be effective? Is a specific **implementation plan** effective? = **not research**; e.g., QI/QA
  - See the IRBO website for guidelines which address QA/QI vs. Research and Program Evaluation vs. Research.

- A project might be designed with both non-research and research objectives.
  - If so, then it would need to be considered **research**.

“Not Research”

- If the purpose of the project is to conduct an evaluation or assessment about an institutional practice, process, or program and use the results internally within an organization or system, it’s likely **not research**.
- *Note: The plan to publish the results does not automatically mean that that project meets the definition of research.*
- The 2018 Common Rule now includes a list of activities that are deemed to be **not research** (45 CFR 46.102(l)(1-4)).

Example of an Activity Determined To Be “Not Research”

- An NCI project is being implemented with the purpose of assessing and improving the current onboarding process for Advanced Practice Providers (NPs and PAs) at NIH.
- Aim is to create an evidence-based onboarding curriculum toolkit that will improve the experience for APPs and that can be used as a foundation for future onboarding programs within NIH.
  - The toolkit will include effective onboarding strategies that have been established in other settings.
- NIH employees will assess current practices and evaluate the toolkit through anonymous surveys using Qualtrics.

Question #2: “About Living Individuals”

If the activity is research:

- Question #2: Does the research involve obtaining information or biospecimens ***about living individuals***? (45 CFR 46.102(e)(1))
  - Is the information **about** humans, i.e., the data being received is **specific to the individual**?
    - Examples of projects which are **not about** i**ndividuals**: surveys about practices and policies in one’s place of work; practices within their field of medicine; or about one’s medical school program.

Not “About Living Individuals”

- Is the information about humans who are still **alive**?
  - If the project only involves data or biospecimens (e.g., cadavers, autopsy biospecimens) from **deceased** individuals, **the research does not involve human subjects** under 45 CFR 46.

- If the research does not involve obtaining information or biospecimens ***about living individuals***, the activity would be considered “not human subjects research”.

Question #3: “Intervention or Interaction”

If the research does involve obtaining information or biospecimens **about living individuals:**

- Question #3: Does the research involve obtaining information or biospecimens **through intervention or interaction** with the individual for use, study or analysis? (45 CFR 46.102(e)(1)(i))?
  - Note: Using web-based platforms (e.g., Amazon MTurk, Qualtrics, Survey Monkey) to collect research data is still considered to be **an interaction**, even though the investigator may never **directly interact** with the subjects.
  - If **yes**, the activity would be considered “research involving human subjects” that is covered by the regulations.

Question #4: “Identifiable Private Information or Biospecimens”

If the research **does not** involve obtaining information or biospecimens **through intervention or interaction** with the individual for use, study or analysis:

- Question #4**:** Does the research involve obtaining, using, studying, analyzing, or generating **identifiable private information or identifiable biospecimens**? (45 CFR 46.102(e)(1)(ii))
  - Note: Coded data or biospecimens are considered identifiable, when the investigator, using, studying, analyzing or generating them, **has access to the code key** linking to identifiers.
  - If **yes**, the activity would be considered “research involving human subjects” that is covered by the regulations.
  - If the answer to both Questions #3 & #4 is **no**, the activity would be considered “not human subjects research”.

Example of an Activity Determined To Be “Not Human Subjects Research”

- An NCI research team would like to implement a project to perform the first comprehensive combined genomic and epigenomic characterization of prostate cancer bone metastases.
- The research team will receive coded frozen or fixed tissue from surgical resections and treatment outcome data from the Zucker School of Medicine and perform DNA, RNA, and chromatin extraction.
- They will have no way to link the samples or data to subject identifiers.
- The team will return results to the external collaborators who will be able to link them to the subjects.
- While this collaboration may constitute human subjects research on the part of Zucker SOM, NCI will not be conducting human subjects research in this case.

No HRPP Requirements for “Not Research” or “NHSR”

- If a project falls under the category of “not research” or “not human subjects research”, it does not require a determination from the IRBO.
- Investigators are allowed to make these determinations themselves but should consult with the IRB, if there is any question.
  - The one exception is if the investigator is conducting a public health surveillance activity. Determinations that these types of activities are **not research** must be made by the Office of Science Policy. Please contact the IRB for more information and see the following notice.
- If an investigator needs a formal determination that their project is “Not Research” or “Not Human Subjects Research”, they can still submit the “Not Human Subjects Research Submission Form” in the electronic IRB system. See the instructions here.

Question #5: Is the Human Subject Research (HSR) Eligible for An **Exemption**?

If the research **does involve human subjects:**

- Question #5: Could the human subject research (HSR) be eligible for **an exemption** (45 CFR 46.104) from IRB review under the revised Common Rule?
  - **Exempt Human Subjects Research**: An activity that meets the definition of human subjects research and meets the criteria under one or more exemption categories as described in the Common Rule. The research is considered so low risk that it does not need meet the criteria for IRB review and approval as delineated in the Common Rule.

New Categories & New Criteria

- The pre-2018 Common Rule included six categories of exempt human subjects research (HSR).
- The 2018 Common Rule includes eight categories of exempt human subjects research.
  - Under these regulations some new exemption categories were added, as well as some new criteria were added to the previous categories.
  - Only six of these exemption categories are currently allowable in the NIH IRP.
  - Only about four of these categories are applicable to NIH research, given the type of research we conduct, i.e., Exemption Categories 1 – 4.

Exempt Determinations

- At the NIH, only the IRBO can make exempt determinations.
  - These are made by IRB Chair designees in the office. Currently those individuals are the Team Leads who are also Expedited Reviewers.
- At times, a project may be eligible for an exemption under a combination of exempt categories.
- In order to receive an exemption, all procedures involved in the project (i.e., protocol) must meet the criteria under one or more exempt categories.
- Even though the protocol might not need to meet the human subject protection requirements under the regulations, there are policy requirements for the conduct of exempt studies at NIH, given our status as an AAHRPP-accredited site.

Key Criteria under Exemption Category 1

- Involves **only** studying normal educational practices, such as research on instructional techniques already in use, in established or commonly accepted educational settings
- Research must not have a likelihood of adversely impacting the student's opportunity to learn required educational content or the assessment of educators who provide the instruction
- The collection and maintenance of identifiable information is permissible.
- Cannot be applied to research that targets prisoners (Subpart C)

Example of NIH Research Approved Under Exemption Category 1

- The NIH Critical Care/Pulmonary Fellowship Program includes annual mastery level learning training on mechanical ventilation.
  - The training involves classroom discussions, simulations, and one-on-one coaching at an initial time point and then six months later.
  - Multi-site research project (involves Critical Care/Pulmonary Fellowship Programs at the NIH CC, MedStar Washington Hospital, Walter Reed, Univ. of Maryland, and University of Pittsburgh) in which NIH receives de-identified data from the other sites
- Objective is to assess the effects of mastery level training on mechanical ventilation among fellows in the program
- Involves a written pre-test and re-test 9-12 months after the training
  - Also collect demographic data and the number of ventilation procedures completed by each fellow

Key Criteria Under Exemption Category 2

- Involves **only** educational tests, surveys, interviews and/or the observation of public behavior
  - Public behavior refers to behavior taking place in a publicly accessible location in which the subject does not have an expectation of privacy (e.g., a public plaza or park, a street, a building lobby, a government building).
- May include the collection and maintenance of sensitive, identifiable information from subjects, **if** the protocol includes a plan to protect the privacy and confidentiality of the subjects
  - Requires a special review by an IRB member (Expedited Reviewer) called “limited IRB review” to ensure the plan is adequate

Key Criteria Under Category 2, cont.

- **Cannot be applied** to research that also involves the use of existing, identifiable data associated with the subjects
- **Cannot be applied** to research involving surveys, interviews, or focus groups with minor subjects (i.e., those 17 years of age or younger)
- **Cannot be applied** to research which involves the observation of the public behavior of minors, when the researcher also participates in the activities being observed
- **Cannot be applied** to research that targets prisoners (Subpart C)

Example of NIH Research Approved Under Exemption Category 2

- NHLBI research project involving focus groups about experiences as patients with Sickle Cell Disease (SCD) or as parents of children with SCD.
- Subjects are adults.
- Questions include experiences with and opinions about genetic counseling and testing
- Focus groups will be audio-recorded and transcribed.
- The project involves the collection of identifiers, and some of the questions may yield sensitive data.
- The protocol includes a plan to ensure the privacy of subjects and the confidentiality of the data (meeting the criteria for “limited IRB review”).

Key Criteria Under Exemption Category 3

- Involves **only** “benign behavioral interventions” (no biomedical interventions)
  - Examples provided as part of the regulations:
    - Playing an online game
    - Solving puzzles under various noise conditions, or
    - Deciding how to allocate a nominal amount of received cash between the subject and someone else

Key Criteria Under Category 3, cont.

- The intervention must be:
  - Brief in duration (although data collection may take longer);
  - Harmless, painless, and not physically invasive; and
  - Not likely to have a significant adverse lasting impact on subjects or be offensive or embarrassing.
- May include the collection and maintenance of sensitive, identifiable information from subjects, **if** the protocol includes a plan to protect the privacy and confidentiality of the subjects
  - Requires a special review by an IRB member (Expedited Reviewer) called “limited IRB review” to ensure the plan is adequate

Key Criteria Under Category 3, cont.

- Must be limited to collecting data via verbal or written responses, data entry, or audio or video recordings
- Must include a plan to obtain prospective agreement from the subjects to participate in the intervention and provide the data
- Must inform the subjects if the research involves deception regarding the nature or purpose and obtain their agreement to still participate

Key Criteria Under Category 3, cont.

- **Cannot be applied** to research that also involves the use of existing, identifiable data associated with the subjects
- **Cannot be applied** to research with minor subjects (i.e., those 17 years of age or younger)
- **Cannot be applied** to research that targets prisoners (Subpart C)

Example of NIH Research Approved Under Exemption Category 3

- NIMH research project which involves completing tasks using Amazon MTurk, e.g., choosing between different images, digits or letters after learning about potential gains and losses and respective probabilities; viewing the outcome of choices; and completing standardized scales about mood, punishment, reward, and pleasure
- Subjects are adults.
- Data collection limited to data entry and mouse clicks.
- Subjects are informed about the research nature, purpose and procedures and click “I agree” before beginning the research.
- Some questions about mood, e.g., depression, may be sensitive; however, no identifiers are being collected.

Key Criteria Under Exemption Category 4

- Involves **only** secondary research using identifiable private information or identifiable biospecimens
  - Data and biospecimens do not have to be in existence prior to the start of the research, e.g., clinical data or biospecimens could be prospectively collected at another site for another purpose and then shared with the research team.
- **Cannot be applied** to research that targets prisoners (Subpart C)
- **Cannot be applied** to research in which the investigators wish to interact with the research subjects (e.g. contacting them to share results)

Four Subcategories Under Category 4, cont.

- Subcategory #1: The data or biospecimens are publicly available, meaning anyone can access them at any time, e.g., from an open-access website.
  - **Cannot be applied** to research if the research team will use a login and password to access the data (e.g., Facebook, Twitter, Instagram)
    - This would not be considered publicly available data.

or

- Subcategory #2: The data will be recorded by the investigator in a de-identified manner, i.e., no identifiers will be retained by the investigator.
  - **Cannot be applied** to research if the research team will download or maintain identifiers that can be linked to data or biospecimens **for any part of the research process**
  - The investigators must commit to never trying to re-identify.

Four Subcategories Under Category 4, cont.

or

- Subcategory #3: Only applies to HIPAA-covered entities (*NIH is not a HIPAA-covered entity.*)

or

- Subcategory #4: The data were originally collected from humans or generated by the government **for non-research purposes** and are protected under the Privacy Act, e.g., QI data related to handwashing practices collected at NIH.
  - **Cannot be applied** to data that was originally generated or collected for research purposes

Example of NIH Research Approved Under Exemption Category 4

- NCI research designed to investigate response free survival at 6 months, following CD19 CAR infusion, in patients with prior chemo vs. none.
- Involves only a medical record review at NIH and other institutions to capture demographics, disease status, prior chemotherapy, response, relapse, overall survival and other clinical data
  - Outside collaborators will also send their de-identified data to NCI as part of this project
- No identifiers will be recorded, and the NIH researchers conducting the project will not be able to re-identify the subjects after the chart review is complete.
  - Protocol states that subjects will not be contacted or re-identified.

HSR That Is Eligible For An Exemption

- If you think that your project may fall under an exemption category(ies) and meets all the associated requirements, you should submit a protocol for consideration of a determination of an exemption.
- Two protocol templates for exempt research (primary data collection & secondary research) can be found here.
  - Be sure to carefully review the *Instructions* for submitting the protocol and the preface of the protocol template to be sure that all required content and attachments are included.

HSR That Is Not Eligible for An Exemption

- If a research project involves the type of research or data collection procedures in the preceding slides, but the design of the study does not strictly meet all the required criteria under the exemption categories, a protocol must be submitted for IRB review and approval instead.

Examples Of HSR That Are Not Eligible For An Exemption

- Conducting surveys, interviews, focus groups, or “behavioral interventions” with minors under the age of 18
- Research involving deception without informing the subjects and seeking agreement
- Any interventions with subjects that involve the collection of data other than in the form of verbal or written responses, data entry, or audio or video recordings
- Any interventions that might be painful, physically invasive, offensive or embarrassing
- Biomedical interventions, e.g., collecting biospecimens, clinical procedures, the use of drugs or devices
- Secondary research analysis of identifiable data or biospecimens, unless publicly available or originally generated by the government for non-research purposes

Test Your Knowledge

Q. 1: What year were institutions, conducting federally-funded human subjects research, required to comply with the revised Common Rule?

A. 2018
B. 2020
C. 2019

Answer: C. 2019

The revised Common Rule became effective in 2018, but full compliance was not required until January 21, 2019.

Q. 2: What is an example of an activity that *most likely* would *not be considered* research under "the Common Rule"?

A. A survey of leukemia patients studying their experiences with palliative care in U.S. hospitals

B. A chart review comparing the outcome of standard chemotherapy vs. a new treatment used off-label for a certain type of cancer.

C. A QA project focused on improving rates of handwashing within an inpatient unit in a hospital

Answer: C. A QA project focused on improving rates of handwashing within an inpatient unit in a hospital

When an activity is being implemented with the purpose of assessing (or improving) a practice, which has been proven to be effective, within a specific institution, it is usually not considered research.

Q. 3: What is an example of an activity that would *not be considered* human subjects research under "the Common Rule"?

A. A survey of leukemia patients studying their experiences with palliative care in U.S. hospitals

B. A secondary research study involving the use of anonymized plasma samples along with clinical data from minor patients

C. A medical chart review comparing the outcome of standard chemotherapy vs. a new treatment, used off-label, for a certain type of cancer

Answer: B. A secondary research study involving the use of anonymized plasma samples along with clinical data from minor patients

If the research involves the use of samples or data collected for another purpose, and the research team has no ability to identify the patients, the activity is considered “not human subjects research”.

Q. 4: What is an example of an activity that involves primary collection of data from subjects that might be eligible for an exemption under “the Common Rule”?

A. A study involving focus groups, physical exams, and medical record review with adult patients treated for bile duct cancer

B. A survey of adult leukemia patients studying their experiences with palliative care in U.S. hospitals

C. Online surveys and qualitative interviews with patients, age 15 or older, who have been diagnosed with Dyskeratosis Congenita

Answer: B. A survey of leukemia patients studying their experiences with palliative care in U.S. hospitals

If the research involves the use of medical interventions or procedures, the activity requires IRB review and approval.

If the research involves surveys or interviews with minors, the activity requires IRB review and approval.

Q. 5: What is an example of an activity that involves secondary research that might be eligible for an exemption under " the Common Rule"?

A. A medical chart review comparing the outcome of standard chemotherapy vs. a new treatment, in which the data is recorded by the investigator without identifiers

B. A secondary research study involving the analysis of identifiable plasma samples; the investigator will need to link the results of the data to other clinical records but will anonymize the results once the linking is complete

C. A new analysis of de-identified data that the investigator has collected under a closed IRB-approved protocol; the investigator will maintain a code key with identifiers but promises he won't access it during the research.

Answer: A. A medical chart review comparing the outcome of standard chemotherapy vs. a new treatment, in which the data is recorded by the investigator without identifiers

If the research involves the analysis of data or specimens while the investigator can still re-identify the subjects (link the data or specimens to identifiers), the activity requires IRB review and approval.

Questions from the Audience

For questions, please contact your Team Lead, Patty Sweet, patricia.sweet@nih.gov, the IRBO mailbox at IRB@od.nih.gov, or OHSRP at (301) 402-3713. You can also find helpful information on the OHSRP website.