Determining Whether Your Project Might Require an Exemption or IRB Review, Including Submission of a Secondary Research Protocol

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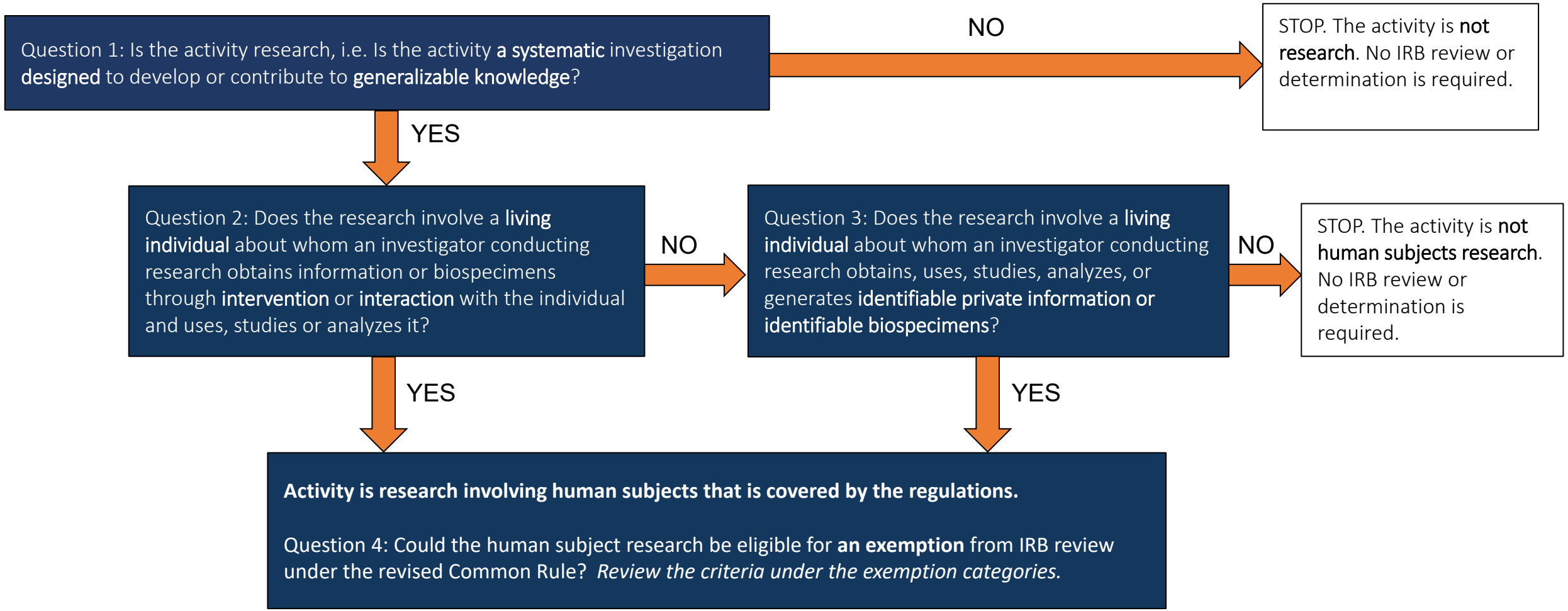
Background

- The DHHS Regulations for the Protection of Human Subjects Research (45 CFR 46) went into effect beginning July 14, 2009.
- Subpart A of these regulations is also referred to as “the Common Rule”.
  - This subpart was revised and required compliance as of January 21, 2019.
  - It is referred to as the 2018 Common Rule (or the Revised Common Rule), while the prior Common Rule is now referred to as the Pre-2018 Common Rule.

Does your Planned Activity Require Submission for IRB Review or Consideration of an Exemption?

Is The Activity Research Involving Human Subjects?



Question 1: Is the activity research, i.e. Is the activity **a systematic** investigation **designed** to develop or contribute to **generalizable knowledge**? (45 CFR 46.102(l))

Is the Activity Research?

- Does the project include a **research objective or a hypothesis**?
- Is the activity conducted in a **systematic** fashion, i.e., done or acted according to a fixed plan or system; methodical in procedure or plan?
- Does the **design** allow the results to be **generalized** to a population beyond just those who were included in the project?
- Is the purpose of the project to contribute to **generalizable knowledge** about certain class or category of subjects in the U.S. or world?

Examples of Activities* Which May Not Be Considered Research under the Common Rule

• Quality Assurance/Quality Improvement (see QA/QI vs. Research) • Program Evaluation (see Program Evaluation vs. Research) • A Case Report involving three or less patients, when data was initially collected for the purposes of diagnosing an individual's condition or for instructional purposes	• Clinical Consulting • Evidence-Based Practice • Public Health Surveillance • Use of an existing sample(s) to validate an assay

*The 2018 Common Rule now includes a list of activities that are deemed not to be research (45 CFR 46.102(l)(1-4)).

“Not Research”

- Note: The plan to publish the results does not automatically mean that that project meets the definition of research.
- **If the project does not meet the regulatory definition of research, then there are no regulatory or policy requirements.**
  - The investigator does not need to submit for a formal determination, IRB exemption, or IRB review.

Question 1: Is the activity research, i.e. Is the activity **a systematic** investigation **designed** to develop or contribute to **generalizable knowledge**? (45 CFR 46.102(l))

If yes, you should move on to Question 2.

If the activity is research:

Question 2: Does the research involve 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 it? (45 CFR 46.102(e)(1)(i) and (2)-(3))

Intervening or Interacting with Living Individuals to Obtain Information or Biospecimens for Research Purposes

- If **yes**, the activity would be considered "research involving human subjects" that is covered by the regulations. Submission for IRB review and approval or an exemption is required. Note:
  - Identifiers would not need to be maintained for the activity to be considered humans subjects research.
  - Collecting data from subjects online using web-based platforms, like Amazon mTurk, Qualtrics, or Survey Monkey, is considered to be **an interaction** and also human subjects research.

If the activity does not involve intervening or interacting with living individuals for research:

Question 3: Does the research involve a **living individual** about whom an investigator conducting research obtains, uses, studies, analyzes, or generates **identifiable private information or identifiable biospecimens**? (45 CFR 46.102(e)(1)(ii) and (e)(4)-(6))

Obtaining Identifiable Private Information or Biospecimens about Living Individuals

- If **yes**, the activity would be considered "research involving human subjects" that is covered by the regulations. Submission for IRB review and approval or an exemption is required.
  - *Note: Coded data or biospecimens are considered, when the investigator, using, studying, analyzing or generating them,* ***has access to the code key*** *linking to identifiers.*

If All Subjects are Deceased or Data/Specimens are De-Identified

- If the project only involves data or biospecimens from deceased individuals*, the research **does not involve human subjects** per 45 CFR 46.
- If the project only involves anonymized or coded (with no access to the code key) data or biospecimens, the research is **not human subject research**.

* Note: there are special regulatory and policy requirements for acquiring and using fetal tissue for research. See the Sourcebook.

No HRPP Requirements for “Not Research” or “Not Human Subjects Research”

- If an activity falls into the category of “not research” or “not human subjects research”, **then there are no regulatory or policy requirements*.**
  - The investigator does not need to submit for a formal determination, IRB exemption, or IRB review.
  - Investigators are allowed to make these determinations themselves but should consult with the IRB, if there is any question.

*Note: 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.

Submitting for a Determination of “Not Research” or “Not Human Subjects Research”

- If you need a formal determination that your project is “Not Research” or “Not Human Subjects Research”, submit a request in the eIRB system, PROTECT.
- Complete the Not Human Subjects Research Application.
- The lead researcher will need to be an NIH FTE and have a PROTECT account. Requests for new accounts can be obtained here.
- Select “Create New Study” in PROTECT and answer all the questions
  - Upload the NHSR Application where it says “Protocol” and be sure to include “NHSR” when naming the document.
- For more information, please see Not Human Subjects Research on the OHSRP website.

If the activity does involve intervening or interacting with living individuals or obtaining identifiable private information or biospecimens for research:

Question 4: Could the human subject research be eligible for **an exemption** from IRB review under the revised Common Rule? (45 CFR 46.104(d)(1)-(8))

Exempt Human Subject Research

Question 4: Is the Human Subject Research (HSR) Eligible for An **Exemption**?

- **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.
  - 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.

Exemption Categories

- Research which might qualify for an exemption is still human subjects research.
- The 2018 Common Rule includes eight categories of exempt human subjects research.
  - The DHHS Office of Human Research Protections (OHRP) has created decision charts to help researchers determine if their project might qualify for an exemption.
- At times, a project may be eligible for an exemption under a combination of categories.

Exempt Determinations

- Only six of the exemption categories are currently allowable at NIH, based on the regulations and policies.
  - Only about four of the categories are commonly used at the NIH.
- If a research project might be exempt, a protocol (and other supporting materials as applicable) must be submitted in the eIRB system for a formal determination.
  - There are additional NIH requirements associated with the conduct of exempt studies that must be addressed in the protocol and followed, in order to maintain our AAHRPP-accreditation.
- Designated staff in the IRBO review these projects and make exempt determinations.

Submitting for an Exemption

- The lead researcher should create a protocol using the applicable exempt research template (prospective data collection from humans or retrospective data or biospecimen review) as well as consent language, recruitment materials, etc. as applicable.
  - Please see Exempt Research on our website for important information about submitting and conducting exempt research.
- The lead researcher will need to be an NIH FTE and have a PROTECT account. Requests for new accounts can be obtained here.
- Select “Create New Study” in PROTECT and answer all the questions
  - Upload the protocol and be sure to include “Exempt” in the title when naming the document.
  - Carefully review the *Instructions* and the preface of the protocol template to be sure that all required content is included and supporting documents are uploaded.

Exemption Categories 2, 3, & 4

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 incorporates other 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)

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 incorporates other 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.

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.
  - Subjects will not be contacted or re-identified.

HSR That Is Not Eligible for An Exemption

- If a research project does not strictly meet all the required criteria under one or more exemption categories, an interventional or observational research 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

Secondary Research

Secondary Human Subjects Research (HSR)

- Definition of **Secondary Human Subjects Research**: Research use of data (or biospecimens) for other than the original purpose(s) for which they were initially collected through interaction or intervention with living individuals.
  - When investigators have access to identifiers and plan to conduct new human subjects research (*not addressed in the original protocol and consent form*) with existing, identifiable data or biospecimens.

Common Examples of Secondary HSR

- Analyzing *existing* identifiable specimens or data to meet a new research objective
- Sharing *existing* coded specimens or data with a collaborator and receiving individual-level results* as part of a new research project

* *Which can be linked to identifiers*

IRB Approval for Secondary Research

- If the investigator will conduct new research using existing identifiable specimens and data, *generally* he or she is expected to submit a new research protocol and seek IRB approval.
- The lead researcher should create a protocol using the applicable protocol template for secondary research.
  - Please see Secondary Research on our website for FAQs about submitting and conducting secondary research.

Prior Informed Consent

- There must be a discussion in the protocol about what the original subjects consented to in the past, if applicable.
- Researchers are expected to review all previous versions of consent forms to determine “who” consented to “what”.
- If the data or specimens were originally conducted with informed consent, the new research plan must comply with the terms of the original informed consent document.

Problem with Prior Informed Consent Language

- If there is language in the original consent form which conflicts with the research plan, you cannot proceed:
  - Examples: statement about destruction of specimens or data; statement about materials only being used for a specific type of research; statement about specimens or data never leaving the NIH; or when one or more subject(s) opted out of future research.
- If the original consent form included language which is contrary to your research plan, you have the option to locate and re-consent the subjects to be able to move ahead with the project.

New Informed Consent or a Waiver is Required

- The new protocol must also address:
  - A plan to obtain consent from original subjects to use the specimens or data for the specific new research (even when there is no conflict with the previous consent forms);

    or

  - A request for a waiver of consent for the new research along with evidence that the criteria for a waiver has been met.

Questions

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