

Doing Research with Data and Biospecimens Under the Common Rule Part 1 – What Researchers Should Know

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Disclaimer

The opinions expressed are those of the presenter and do not necessarily reflect the policy of the U.S. Department of Health and Human Services.

For a complete and accurate description of the regulatory requirements, please refer to the text of the regulations available on [OHRP's website](#).



Overview

This presentation on research with data and biospecimens will focus on the concept of secondary research. We will assume the research is funded by the Department of Health and Human Services (HHS).

Outline:

- What secondary research is and how to distinguish it from primary research
- What *identifiable* means under the Common Rule (CR)
- How CR applies to secondary research with data and biospecimens

Concept of Secondary Research

The research use of information or biospecimens originally acquired for:

- **Non-research purposes**
(e.g., information collected for routine clinical care; leftover blood from routine clinical tests; information collected for Medicaid billing), **OR**
- **Research studies other than the proposed one**
(e.g., information collected for a drug study on Alzheimer's now being used to study if early-onset diabetes predisposes an individual to Alzheimer's development)

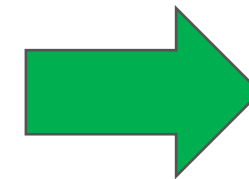


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The Concept of Primary Research and the Regulatory Definition of *Human Subject* at §46.102(e)(1)

Regulatory definition for ***Human Subject***: a living individual about whom an investigator conducting research

1) **Obtains information or biospecimens *through intervention or interaction*** with the individual...;



- Human subjects research
- Primary research
- Needs IRB review (and likely informed consent) unless the whole research meets the conditions for one or more exemption categories in the Common Rule

More on the Concept of Primary Research

- It is primary research if the activity (obtain ... through intervention or interaction) is conducted on the behest of the investigator for the purpose of the research being proposed.
 - It doesn't matter if the actual research interaction or intervention is carried out by another group of investigators, a commercial enterprise, or otherwise.
- Even if the intervention is a common clinical procedure, if it is carried out specifically for the purpose of the research, the activity will be considered primary research.
- It is also primary research when, for example, additional biospecimens are collected for research purposes at the time of a procedure done for clinical care.

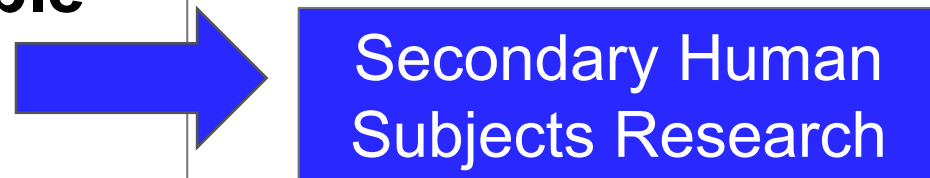
The Concept of Secondary Research and the Regulatory Definition of *Human Subject* at §46.102(e)(1)

Regulatory definition for ***Human Subject***: a living individual about whom an investigator conducting research

1) Obtains information or biospecimens ***through intervention or interaction*** with the individual...;

OR

2) Obtains, uses, studies, analyzes, or generates ***identifiable private information or identifiable biospecimens***



More on the Concept of Secondary Research

- There is NO interaction or intervention with individuals specifically to collect their data or biospecimens for the purpose of the proposed research.
- Hence, secondary research is simply research with data and biospecimens and CR considerations focus primarily on the investigators and the sources of the data/biospecimens for their research.
- Typically, CR considerations are not applicable to the supplier of the materials, if supplying is their **only role**.
 - When applying CR, don't call these suppliers collaborators to avoid confusion!
- *Identifiability* is what makes this kind of research also human subjects research.

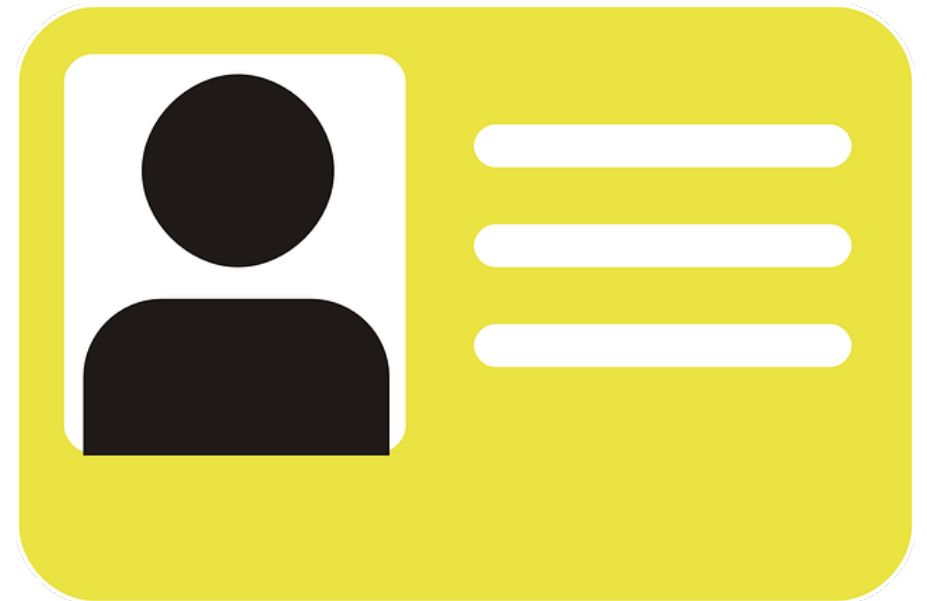
What Does *Identifiable* Mean Under the Common Rule?

Identifiable private information or *identifiable biospecimens* refers to private information or biospecimens **for which the identity of the subject**

- ***is or may readily be ascertained by the investigator, or***
- ***[is] associated with the*** information or biospecimens §46.102(e)(1)
- The Common Rule does not define other associated terms, such as *coded*, *de-identified*, or *anonymized*
- It does not have a list like the “HIPAA identifiers”
- Unique identifiers may not necessarily be “identifiable” under the Common Rule
- OHRP generally considers facial images and voice recordings of individuals as identifiable

Identifiable Under the Common Rule

- This presents a **subjective standard** requiring consideration of the details of the research. Determination will vary from case to case.
- Essentially, one is looking to see if the data and/or biospecimens can be readily linked back to a living individual by the investigators.

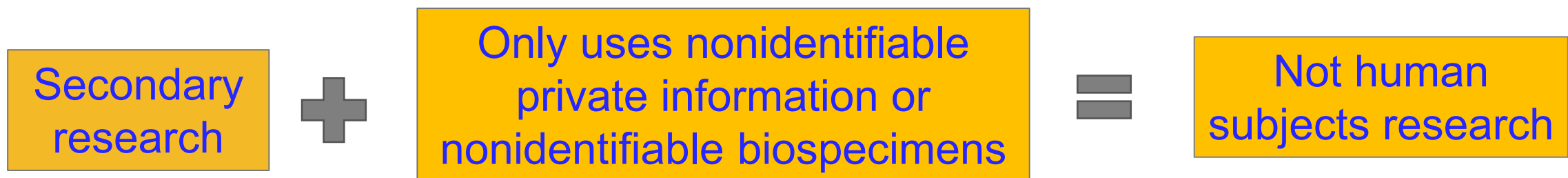


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Secondary Research with Coded Materials: When is it Not Human Subjects Research?

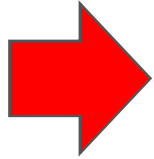
When research involves **only** coded private information or coded biospecimens **and** meets both of the following:

- 1) Investigators (including any associates on the research) do not interact or intervene with subjects to collect the materials for the purpose of this research, **AND**
- 2) Investigator(s) cannot readily ascertain the identity of the individual(s) to whom data/specimens pertain



Secondary Research with *Identifiable* Materials is Human Subjects Research – Check for Exemption Categories

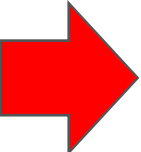
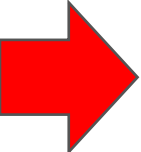
Main Exemption Categories for *Secondary Research Involving Human Subjects* (§46.104(d))



- **Exemption 4: Secondary research use of identifiable biospecimens or private information**
- Exemption 5: Evaluation of public benefit and service programs
- Exemption 7: Storage and maintenance of identifiable materials for unspecified secondary research with broad consent
- Exemption 8: Secondary research use of stored identifiable materials with broad consent

Exemption 4: Main Exemption for Secondary Research Use of *Identifiable* Information or *Identifiable* Biospecimens

Exemption 4 ([§46.104\(d\)\(4\)](#)) applicable if:

- i. Identifiable materials are publicly available, **OR**
- 
 ii. Information, which may include information about biospecimens, is **recorded** by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, and **the investigator does not contact the subjects or re-identify subjects, OR**
- 
 iii. Investigator's use is regulated under HIPAA as "health care operations," "research," or "public health," **OR**
 - This means no need to worry about Common Rule, just follow HIPAA
 - Note - HIPAA only applies to information, not biospecimens
- iv. Research is conducted by, or on behalf of, a Federal agency using data collected or generated by the government for nonresearch purposes, and the information is protected by federal privacy standards

Reminder About Exemption Categories

- For human subjects research to be exempt, the whole project must meet the conditions for one or more exemption categories.
- For cooperative research that comes under the single IRB review mandate at §46.114, do NOT even consider exemption categories. They are **nonexempt human subjects research** projects!
 - However, it is possible that some collaborating institutions may not be doing human subjects activities, and hence, are considered *not engaged*.

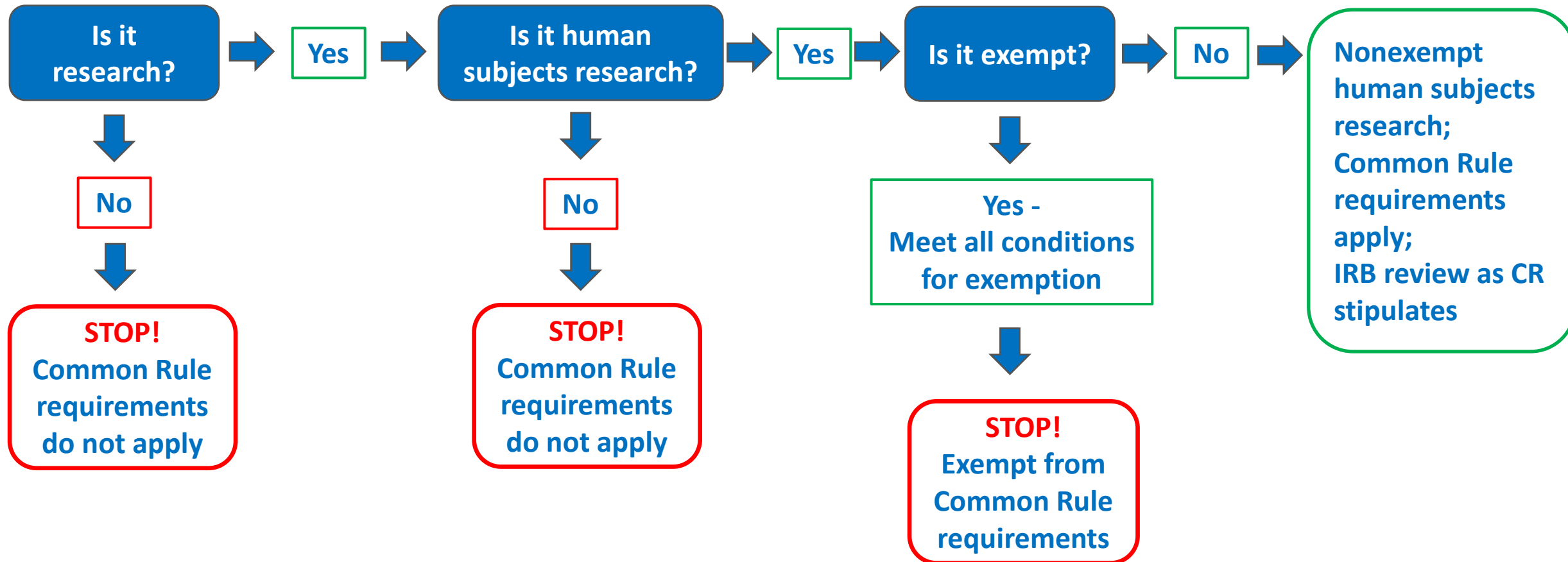
Human subjects research that meets the conditions for one or more exemption categories



Investigators/Institutions have **Flexibility for review and consent** outside the regulations

Ethical responsibilities for participants' rights & welfare remain!

Flowchart Showing How to Determine if a Project is *Nonexempt Human Subjects Research*



Scenario 1

Researchers contact a large medical center to obtain a dataset on the frequency and distribution of certain diagnostic codes used in their electronic medical records to study the implications of moving from one version of ICD codes to the newest version.

Analysis:

1. Is this secondary research?
 - Yes, this **is secondary research** because the information is not originally collected specifically for the purpose of the investigator's research. There is no interaction or intervention done specifically for the research.
2. Is this secondary research *human subjects research*?
 - No, this secondary research **is not human subjects research** because the dataset that the investigators will receive for the work does not include individually identifiable information.

Scenario 2

A team of data researchers is given access to individually identifiable patient data in electronic medical records to conduct the research. The team will only record data that cannot be linked back to living individuals. They will not have means to contact individuals and agree not to re-identify the data.

Analysis:

1. Is this secondary research?
 - Yes, this **is secondary research** because the information is not originally collected specifically for the purpose of the investigator's research. There is no interaction or intervention done specifically for the research.

Scenario 2, cont'd

Analysis:

2. Is this secondary research *human subjects research*?
 - Yes, this secondary research **is human subjects research** because investigators have access to individually identifiable data for their research.
3. Does this secondary human subjects research need to comply with CR requirements including formal IRB review? Or, Does the entire research meet one or more exemption categories?
 - This is secondary human subjects research that meets the conditions for exemption 4 at §46.104(d)(4(ii) and therefore, does not need to comply with other CR requirements such as IRB review or informed consent.

Scenario 3

Hospital A agrees to provide a team of bench scientists with sputum and lung aspirates leftover from clinical procedures involving chronic smokers. The hospital will provide the specimens without any individually identifiable information and will not be otherwise involved in the research. The research team will conduct whole genome sequencing of the specimens as part of their research.

Analysis:

1. Is this secondary research?
 - Yes, this **is secondary research** because the biospecimens were originally collected for clinical care and not specifically for the purpose of the investigator's current research. There is no interaction or intervention done specifically for the research.

Scenario 3, cont'd

Analysis:

2. Is this secondary research *human subjects research*? Are the biospecimens identifiable?
 - The biospecimens do not come with individually identifiable information.
 - The whole genome sequencing procedure may identify something unique to an individual, but the investigators are unlikely to be able to use this to readily link the biospecimens back to the individual.
 - Therefore, not identifiable, hence, **secondary research that is not human subjects research.**
3. Is Hospital A, the supplier of biospecimens, part of the research team?
 - Not under the Common Rule as long as the supplier does not have any other role or intellectual input into the research.
 - Don't call them collaborators and don't offer "gift authorship."

Scenario 4

An investigator wants to review aggregate data for buprenorphine prescriptions to patients with opioid use disorder who present to hospital ERs. She wants to see if a checklist she implements for ER physicians to use when treating patients with the disorder would increase the prescription rate and improve care for these patients.

Analysis:

1. Is this secondary research?

- The investigator asks to review data that are routinely collected.
- BUT, her research interest involves a difference in prescription rate as a result of an intervention that she introduces for the research.
- This is **PRIMARY human subjects research!**
- Don't just look at the source of the data the investigators are getting for their analysis. Typically, research has a hypothesis and certain outcome expectations. You need to know this to make sense of the activities proposed in the research and not jump to erroneous conclusions.

Scenario 5

A team of investigators has refined an intervention that is shown to be effective in blocking the proliferation of animal kidney cancer cells having certain genetic expressions. They want to test the intervention on human kidney cancer cells with the same genetic expressions. They will do this on leftover cancer kidney cells obtained from patients who had participated in an earlier kidney cancer clinical trial that they were involved in. Their physician collaborators will only provide them with coded biospecimens.

Analysis:

1. Is this secondary research?
 - Yes, this **is secondary research** because the biospecimens were not originally collected specifically for the purpose of the investigator's research. There is no interaction or intervention done specifically for the research.

Scenario 5, cont'd

Analysis:

2. Is this secondary research *human subjects research*? Are the biospecimens identifiable?
 - The biospecimens are coded and are provided by physician-investigators with whom they had collaborated on a prior clinical trial
 - (The current research is potentially related to the previous trial)
 - It is quite probable that these investigators are continuing their collaboration with those involved in the previous clinical trial. As part of the research team, they are likely to be able to readily link the biospecimens back to individual participants.

Scenario 5, analysis cont'd

3. Will this secondary human subjects research need to comply with CR requirements including formal IRB review? Does it meet an exemption category? Does it meet the conditions for exemption 4 at §46.104(d)(4(ii) or (iii)?

ii. Information, which may include information about biospecimens, is recorded by the investigator in such a manner that **the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, and the investigator does not contact the subjects or re-identify subjects, OR**

iii. Investigator's use is regulated under HIPAA as "health care operations," "research," or "public health," **OR**

This means no need to worry about Common Rule, just follow HIPAA

Note - HIPAA only applies to information, not biospecimens

Thoughts?

Scenario 5, cont'd

- Will the HIPAA exemption at §46.104(d)(4)(iii) work assuming that all the investigators work in a HIPAA-covered entity?
 - No, because there is analysis of biospecimens, not just the use of data for research
- Will the exemption at §46.104(d)(4)(ii) work since all the research is secondary research?
 - Probably not. Everyone seems to have an enduring interest in the treatment of kidney cancer. Even though the proposed research project is a seemingly independent project, the investigators are likely to want to maintain the ability to link the results back to identifiable individual patient-participants of the clinical trial.
- This will likely be **secondary, non-exempt, human subjects research** that needs to follow CR requirements for IRB review and informed consent, etc.

Scenario 6

A physician investigator of a large methadone center wants to find out if opioid drug users with a particular genetic polymorphism are more likely to relapse on methadone treatment. She will conduct genetic analysis of blood samples leftover from clinical collection and obtain patients' methadone treatment and clinical care information for a year for analysis.

Analysis:

1. Is this secondary research?

- Yes, this **is secondary research** because both the biospecimens and the data are originally collected for clinical purpose and not specifically for the investigator's proposed research. There is no interaction or intervention done specifically for the research.

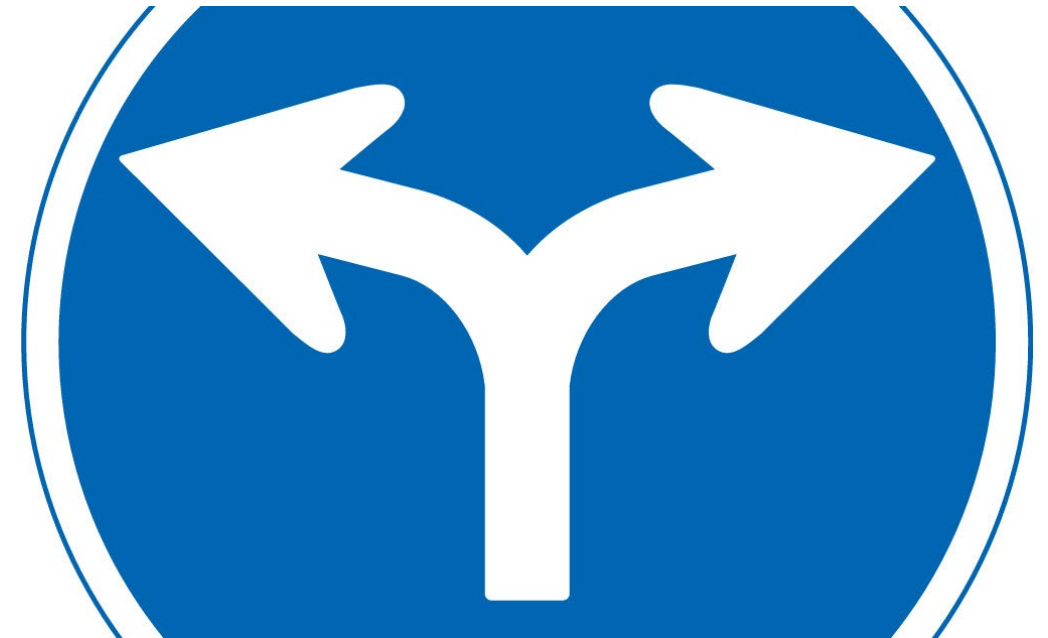
Scenario 6, analysis cont'd

2. Is this secondary research *human subjects research*? Are the biospecimens/data identifiable to the investigators?
 - The biospecimens do not come with individually identifiable information
 - However, the study is longitudinal, and the clinical data need to be linked up with the biospecimens for the purpose of the study.
 - Since the investigator also works at the center, it is quite probable that she will be able to readily link the materials back to individual patients.
 - Therefore, this is likely **secondary human subjects research**
3. This research is also unlikely to meet the conditions for exemption 4. Hence, it'll be secondary, non-exempt, human subjects research requiring IRB review etc.
4. **Question:** Could the use of an honest 3rd party broker help make this secondary research be **not human subjects research**?

What Do the Regulations Require for Human Subjects Research with No Applicable Exemptions?

Typical Requirements (among others):

- The primary awardee and any collaborator institutions conducting the human research activities are covered by Federalwide Assurance (FWA)
- **IRB review** according to regulatory requirements & criteria
- **Informed consent** according to regulatory requirements (unless waived)
- The revised Common Rule added new condition for waiver: that the research could not practicably be conducted without the materials in an identifiable format ([§46.116\(f\)\(3\)\(iii\)](#))



**IRB Review –
Expedited Review Mechanism or Full Board**

IRB Review of Nonexempt Human Subjects Research - Expedited Category 5 is for Secondary Research

When the following conditions are met:

1. Research involving data, documents, records, or specimens that have been collected (***for research or non-research purposes**) or will be collected solely for non-research purposes.
(***not in the regulations but represents OHRP's usual interpretation**)
2. Research procedures must present no more than minimal risk to subjects
3. Include protections for privacy and confidentiality as appropriate

[See Secretary's 1998 List of Research Eligible for Expedited Review](#)

Note:

- Initial review done by a designated IRB member
- With few exceptions, no continuing reviews needed

Summary on Options for Secondary Research with Data and Biospecimens

1. Use non-identified data or biospecimens
2. Meeting the conditions for an exemption
 - Exemptions 4, 5, 7, 8. Exemption 4 is the most commonly used. 7 & 8 require limited IRB review including broad consent at §46.116(d).
3. Obtaining IRB reviews and consent for the secondary use of identifiable materials
 - Consent can be standard consent or broad consent. Standard consent must include sufficient details to meet the requirements at §46.116 (a-c).
4. Obtaining IRB reviews and waiver of consent for the secondary use
 - For waiver at §46.116(f), IRB must find that the research use of identifiable materials could not practicably be carried without the waiver.

Regardless of the applicability and compliance with the regulations, there are ethical considerations and responsibilities to think about!

OHRP Resources

- Guidance documents on research with Biological Materials and Data at www.hhs.gov/ohrp/regulations-and-policy/guidance/biological-materials-and-data/index.html
- Human Subjects Regulations Decision Charts for the 2018 Common Rule Requirements at www.hhs.gov/ohrp/regulations-and-policy/decision-charts-2018/index.html
- Video recordings on secondary research use at www.hhs.gov/ohrp/education-and-outreach/online-education/videos/issues-related-to-type-of-research/index.html

*Thank
You*

Contact us at
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