OFFICE OF THE ASSISTANT SECRETARY FOR HEALTH

Considerations for Registries and Data Centers under the Revised Common Rule

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1

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

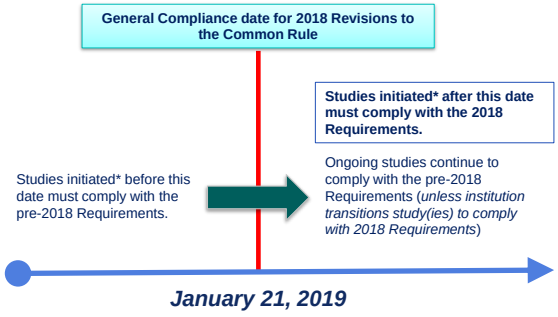
Agenda

- HHS Regulations for the Protection of Human Subjects in Research
- Common Rule Considerations for registries and Data Centers

HHS REGULATIONS FOR THE PROTECTION OF HUMAN SUBJECTS IN RESEARCH

HHS Regulations on Human Research Protections at 45 CFR part 46

- OHRP holds the regulatory authority on the HHS Protection of Human Subjects regulations, 45 CFR 46
- Subpart A is referred to as the Common Rule
- Revisions to the Common Rule made final in 2018 with a compliance date 1/21/2019
  - a.k.a. the 2018 Requirements or revised Common Rule



** Initiated = determined to be exempt, initially approved by an IRB, or granted a Secretarial Waiver*

When Does the Common Rule Requirements Apply?

- Apply to non-exempt human subjects research supported or conducted by a Common Rule Agency

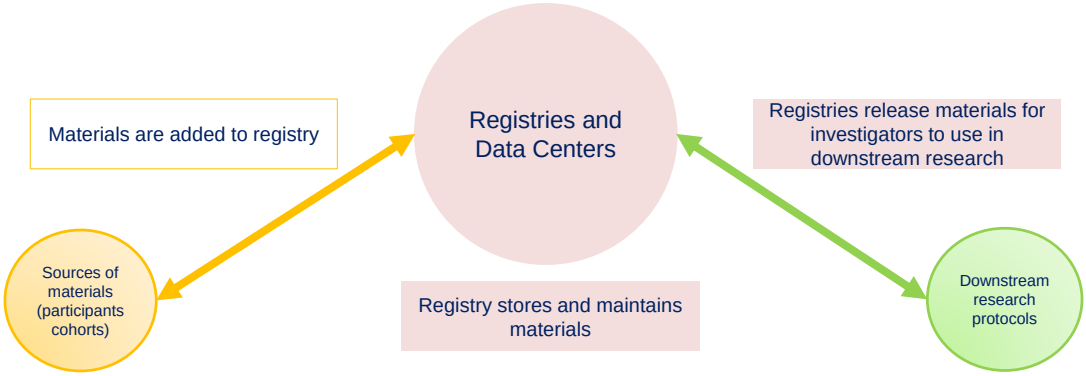
No federal enforcement if not funded by a Common Rule agency. Institutions can choose to come under OHRP's authority when filing FWA.

- To determine if a study is non-exempt human subjects research, ask these 3 questions in this order about the study/research project:

1) Does the activity involve research?
2) Does the research involve human subjects?
3) Is the research with human subjects exempt?

Considerations for Registries: Which Activities Require IRB Approval?

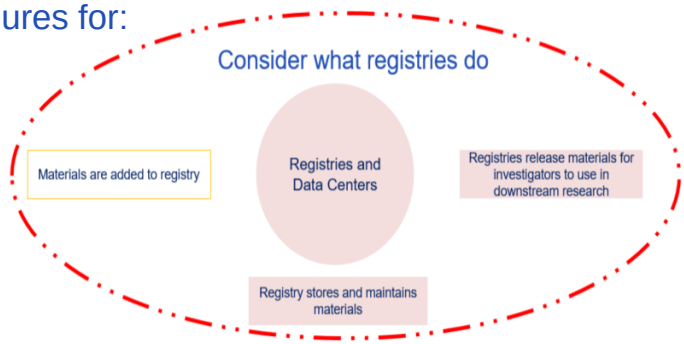
Consider what registries do



Issues to Consider in the Research Use of Stored Data or Tissues (1996, 1997) www.hhs.gov/ohrp/regulations-and-policy/guidance/issues-to-consider-in-use-of-stored-data-or-tissues/index.html

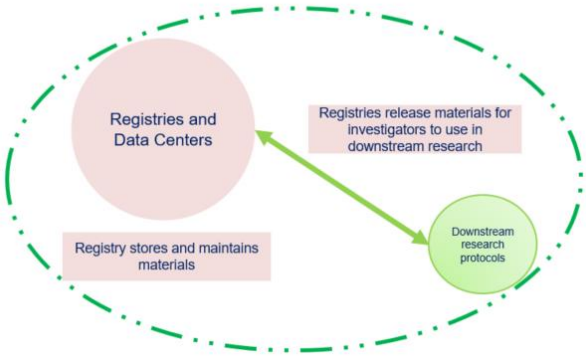
Considerations for Registries: Establishing a Registry

- Three separate activities, each with regulatory and ethical considerations
- Registry will have policies/procedures for:
  - Establishment of the repository
  - Terms for adding information and informed consent
  - Terms for releasing information and informed consent
  - Privacy and confidentiality protections



- Funding usually determines whether Common Rule applies

Considerations for Registries: Downstream Protocols



- After a registry has been established, researchers request or obtain materials from repositories
- Involvement of repository in these downstream activities varies
- Investigators' institutions usually determine whether the Common Rule applies to these activities

1. Does the Activity Involve Research?

Research refers to a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge

- There are 4 types of activities deemed **NOT** to be research:
  1) Scholarly and journalistic activities
  2) Public health surveillance activities
  3) Information collection for criminal justice purposes
  4) Operational activities for national security purposes

§46.102(l)

Exclusion: Public Health Surveillance Activities Deemed Not to Be Research

- Activities conducted, supported, requested, ordered, required, or authorized by a public health authority.
  - *An agency or authority responsible for public health matters as part of its official mandate, or a person or entity under a grant of authority or contracted by such agency* §46.102(k)
- Limited to those necessary to allow a public health authority identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance

§46.102(l)(2)

2. Does the Research Involve Human Subjects?

Human Subject is a living individual about whom an investigator conducting research either:

X Obtains information or biospecimens **through intervention or interaction** with the individual … ; **OR**

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

IF

No interactions or interventions with human subjects for the purpose of the proposed research

AND

Use of non-identifiable or non-private information or biospecimens

Then:

Not human subjects research

- Research use of information/biospecimens originally collected for a purpose other than the proposed research is commonly referred to "**secondary research**."
- **Secondary research that only uses non-identifiable materials is not human subjects research.**

3. Is the Human Subjects Research Exempt?

Exemption 1: Normal educational practices in established educational settings

Exemption 2: Educational tests, surveys, interviews, or observation of public behavior

Exemption 3: Benign behavioral interventions

Exemption 4: Certain secondary research use of identifiable biospecimens or private information

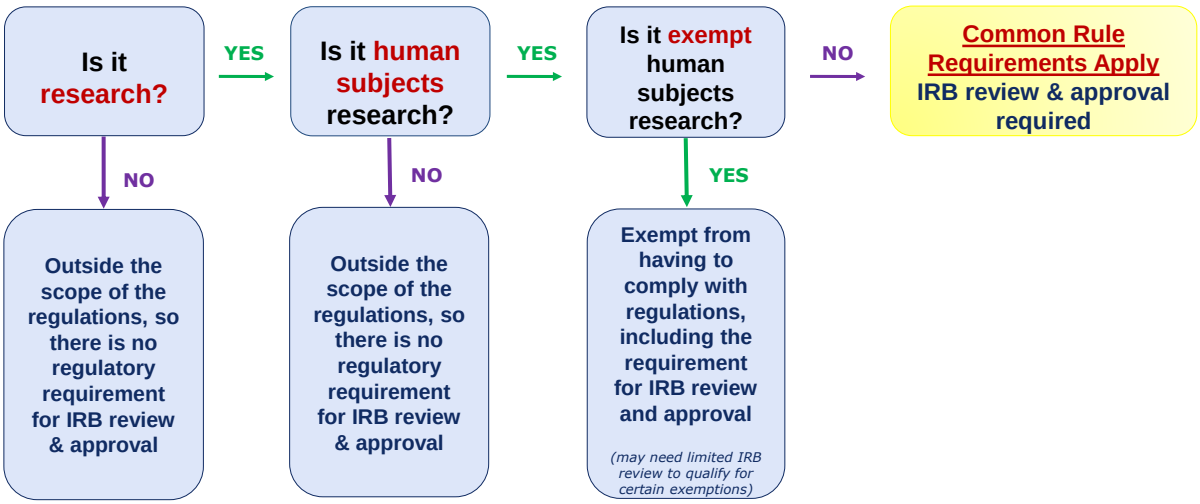
Exemption 5: Evaluation of public benefit and service programs

Exemption 6: Taste and food quality evaluation & customer acceptance studies

Exemption 7: Storage or maintenance of identifiable biospecimens or private information for unspecified secondary research with broad consent

Exemption 8: Secondary research use of stored identifiable biospecimens or private information with broad consent

Determining Whether an Activity is Non-Exempt Human Subjects Research



What About State Requirements for Registries?

- State-mandated requirements must be followed
- If registry activities come under the scope of the Common Rule:
  - IRB review may be required,
  - Compliance obligation under OHRP's purview
- If registry activities DO NOT come under the scope of the Common Rule:
  - No IRB review required by OHRP
  - No compliance obligation to OHRP
- Some states may require IRB approval according to the Common Rule → compliance obligation is to the state, not to OHRP

Common Rule Requirements for Registries When They are Involved in Human Subjects Research Activities

- Registry must have an FWA filed with OHRP
- An **IRB must review and approve** the study, including the registry's research activities
  - IRB may or may not be associated with the registry, but it must be registered with OHRP
  - Cooperative research generally must be approved by a single IRB for research covered by the revised Common Rule
  - Continuing review is required for some non-exempt, human subjects research

(other requirements apply)

Common Rule Requirement for Single IRB Review

- Cooperative research: two or more institutions engaged in non-exempt human subjects research
- U.S. institutions engaged in cooperative research for the portion of the research conducted in the U.S. must rely on the review of a single IRB
- Does not apply:
  - When more than single IRB review is required by law (including tribal law)
  - Whenever any Federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular context

Common Rule Requirement for IRB Review of Research

Protocol review can be either full board review or via expedited mechanism

- Same approval criteria must be satisfied (at 46.111)
- Expedited review can be used when research activities:
  - Present no more than minimal risk to subjects, **AND**
  - Involve only procedures listed in one or more of the categories on the Expedited Review Procedure list
    - **Category 5**: Research involving material that have been collected already, or that will be collected solely for non-research purposes

Continuing Review Not Required in Certain Circumstances

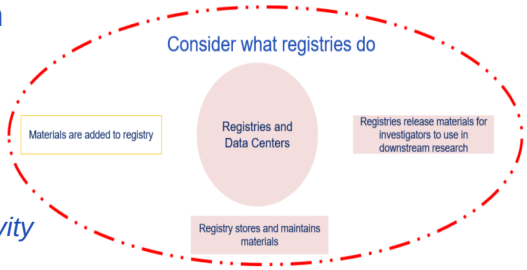
- In general, no continuing review is required for:
  - Research eligible for expedited review
  - Exempt research requiring limited IRB review
  - Research that has completed interventions and only involves:
    - Analyzing data, including analyzing identifiable private information or identifiable biospecimens
    - Accessing follow-up clinical data from clinical care procedures
- IRB can override this default and require continuing review according to the Common Rule, but this must be documented
- Institutions and IRBs can also establish other ways of "checking in" with researchers that are outside OHRP's compliance oversight

COMMON RULE CONSIDERATIONS FOR REGISTRIES AND DATA CENTERS

Considerations for Registries: Registry Functions

Is IRB review required to collect information in a repository?

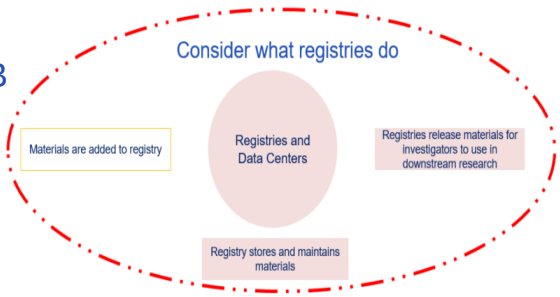
1) Does registry receive HHS funding?
2) Does the registry involve research?
   - *Is research a purpose of the repository?*
   - *Is the repository a public health surveillance activity according to the revised Common Rule?*
3) Does the research involve human subjects?
   - *Are there interactions or interventions with subjects to collect the information for the repository?*
   - *Does repository receive identifiable private information?*
4) Is the research with human subjects exempt?



Considerations for Registries: Registry Functions (*cont.* …)

OHRP's Guidance on Issues to Consider in the Research Use of Stored Data or Tissues (1997)

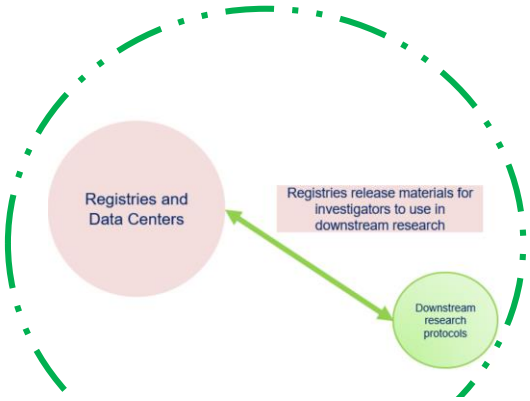
- Operation of data management centers should be subject to oversight by an IRB
- Registry will have policies/procedures for:
  - Establishment of the repository
  - Terms for adding information and informed consent
  - Terms for releasing information and informed consent
  - Privacy and confidentiality protections



www.hhs.gov/ohrp/regulations-and-policy/guidance/issues-to-consider-in-use-of-stored-data-or-tissues/index.html

Considerations for Registries: Which Registry Activities Require IRB Approval for the Purpose of Downstream Research?

- Only releasing materials is not considered involvement in the downstream research (even if identifiable)
- Other regulations (e.g., HIPAA, state mandates) and institutional policies may apply
- Registry release of materials should occur according to its terms and policies/procedures

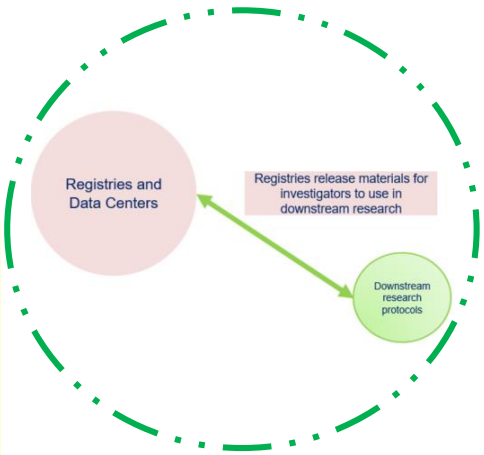


What if the registry is doing more than just releasing materials?

Considerations for Registries: Which Registry Activities Require IRB Approval for the Purpose of Downstream Research? (*cont.* …)

Whether registries' activities for a downstream protocol require IRB approval depends on:

1. Whether the downstream protocol is non-exempt, human subjects research (if not, regulations do not apply, IRB review not required), **and**
2. Whether registry's employees or agents are involved in human-subjects research activities for the downstream protocol
   - Simply releasing identifiable materials to investigators is not considered human subjects research activity



When Are Registries' Employees or Agents Involved in the Human Subjects Research for the Downstream Protocol?

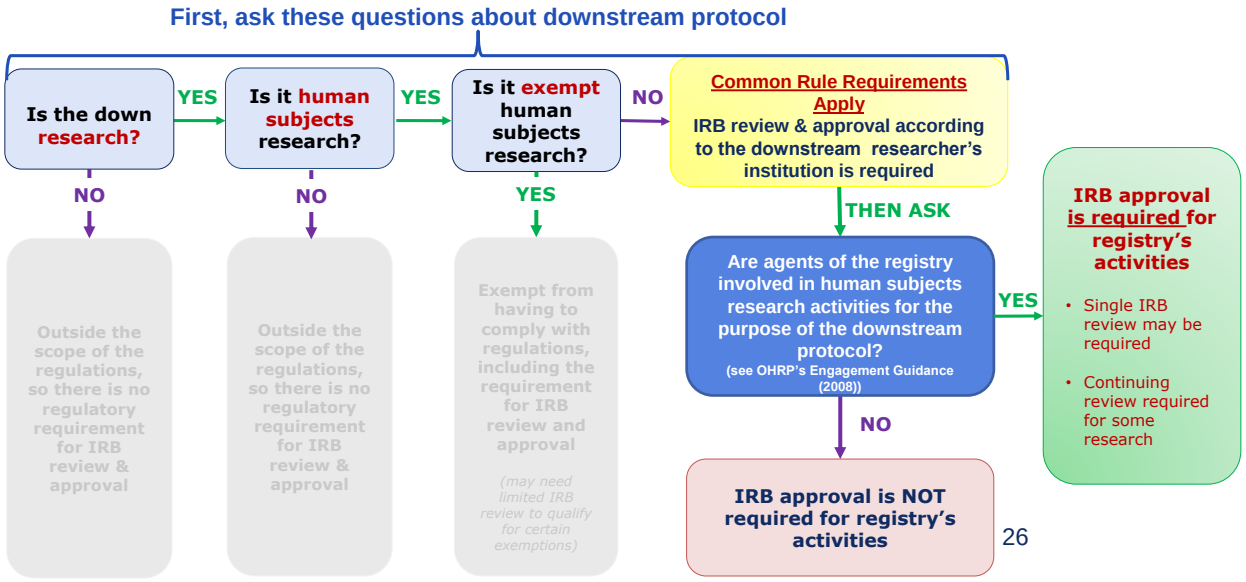
Registry employees or agents are involved in the research when they:

- Are part of the downstream protocol research team
- Obtain for the purpose of (an HHS-funded) downstream protocol:
  - Data about or biospecimens from subjects through **intervention or interaction**; **OR**
  - **Identifiable private information** about the subjects; **OR**
  - The informed consent of human subjects for the research

But, see OHRP's Guidance on Engagement of Institutions in Human Subjects Research (2008) for additional information and some exceptions, such as:

- **Only** releasing materials to downstream investigators
- Asking subjects for permission to be contacted by downstream investigators
  https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-engagement-of-institutions/index.html

Summary: When Would Registry Activities as Part of a Downstream Protocol Require IRB Approval?



Example 1.0

Researchers in an NCI-funded study will administer surveys to subjects once they agree to participate in the study. Researchers will then send the subjects' PII to state cancer registries to check if subjects have been diagnosed with cancer. Registries will only link this information to their data and, if there is a match, release those full identifiable records to the researchers.

Does the researcher's downstream protocol require IRB approval under the Common Rule?

- More information needed: This is likely research with primary and secondary research components (public health surveillance activity?) Likely human subjects. Possibly exempt.

Do registry activities require IRB approval under the Common Rule?

- No. Even if protocol is non-exempt human subjects research, registry is only linking to respond to a request for releasing information to researchers
- Registry release should occur according to the terms and SOPs of the state cancer registry

Example 1.1

Researchers in an NCI-funded study will administer surveys to subjects once they agree to participate in the study. Researchers will then send the subjects' PII to state cancer registries to check if subjects have been diagnosed with cancer. Registries will only link this information to their data and, if there is a match, release those full identifiable records to the researchers, **who will collect blood samples from the matching subjects.**

Does the researcher's downstream protocol require IRB approval under the Common Rule?

- Likely yes. This is likely research involving human subjects, and no exemption seems relevant.

Do registry activities require IRB approval under the Common Rule?

- No. Even if protocol is non-exempt human subjects research, registry is only linking to respond to a request for releasing information to researchers
- Registry release should occur according to the terms and SOPs of the state cancer registry

Example 1.2

Researchers in an NCI-funded study will administer surveys to subjects once they agree to participate in the study. Researchers will then send the subjects' PII to state cancer registries to check if subjects have been diagnosed with cancer. Registries will only link this information to their data and, if there is a match, release those full identifiable records to the researchers. **Researchers will contact subjects for consent to collect tumor samples from their healthcare providers.**

Does the researcher's downstream protocol require IRB approval under the Common Rule?

- More information needed: This is likely secondary research. Likely human subjects. Could be exempt.

Do registry activities require IRB approval under the Common Rule?

- No. Even if protocol is non-exempt human subjects research, registry is only linking to respond to a request for releasing information to researchers
- Registry release should occur according to the terms and SOPs of the state cancer registry

Example 1.3

Researchers in an NCI-funded study will administer surveys to subjects once they agree to participate **and obtain their consent to obtain tumor samples if they develop cancer.** Researchers will then send the subjects' PII to state cancer registries to check if subjects have been diagnosed with cancer. Registries will link this information to their data and, if there is a match, **registry will reach out to subjects' healthcare providers to obtain tumor samples** and then release the full identifiable records to the researchers.

Does the researcher's downstream protocol require IRB approval under the Common Rule?

- More information needed: This is likely secondary research, but it could be a public health surveillance activity. Likely human subjects. Could be exempt.

Do registry activities require IRB approval under the Common Rule?

- If downstream protocol is not exempt, then **registry activities require IRB approval**: registry's employees are obtaining identifiable private information for the purpose of the downstream protocol

Example 2.0

Researchers in an NCI-funded research study ask the registry to provide contact information for breast cancer patients in the registry. The registry will only release the patients' contact information to the researchers. Researchers will ask the patients to join the study and obtain blood samples from those who agree.

Does the researcher's downstream protocol require IRB approval under the Common Rule?

- Likely yes. This is likely research involving human subjects, and no exemption seems relevant.

Do registry activities require IRB approval under the Common Rule?

- No. Only releasing materials to investigators is not considered involved in the downstream research
- Registry release should occur according to the terms and SOPs of the state cancer registry

Example 2.1

Researchers in an NCI-funded research study ask the registry to provide contact information for breast cancer patients in the registry. The registry will contact patients to ask them for permission to be contacted by these researchers. Researchers will then ask patients to join the study and obtain blood samples from those who agree.

Does the researcher's downstream protocol require IRB approval under the Common Rule?

- Likely yes. This is likely research involving human subjects, and no exemption seems relevant.

Do registry activities require IRB approval under the Common Rule?

- No. Only asking subjects for permission to be contacted by downstream investigators is not considered involved in the downstream research
- Registry release should occur according to the terms and SOPs of the state cancer registry

THANK YOU