

**Day one-presentation-session V**  
**Julie Kaneshiro**

**Human subjects: ethical & legal issues/45 CFR 46**

**How does 45 CFR part 46 apply to the creation of a rare disease registry that may be linked to a bio-specimen repository?**

**Julie Kaneshiro**

- Jurisdiction of the HHS human subject protection regulations (45 CFR part 46)
  - Applies to human subjects research conducted or supported by U.S. Department of Health and Human Services (U.S. and non-U.S. institutions)
  - If U.S. institution chooses to apply to all human subjects research through a Federalwide Assurance—applies regardless of source of support
- HHS regulations apply only if: (1) activity involves research; (2) activity involves human subjects; and (3) human subjects research activity is not exempt. These three questions asked for each of the three core activities illustrated below.



- Key questions to assess whether registry/bio-specimen repository is covered by HHS regulations:
  - Is it research?



**Depends**

Obtained for clinical or research purposes?

Obtained for bank?

Obtained for another study?

**Yes**

**Yes**

- Are human subjects involved?





**Depends**

Research intervention/interaction?  
Identifiable private information?

**Depends**

Identifiable private  
information?

Note: “OHRP Guidance on Research Involving Coded Private Information or Biological Specimens”

(<http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf>). Defines when research involving data or specimens does not involve human subjects.

- In sum: Research Repositories & Databases: 3 Paths to Human Subjects Research:
  1. Creating a research repository/database *through intervention or interaction with individual*
  2. Creating a research repository/database *by obtaining identifiable private information*
  3. Obtaining identifiable private information *from a research repository/database*.
- Distinguishing “human subjects research” from “engagement” in human subjects research
- Some key informed consent considerations:
  - If data/specimens obtained for clinical purposes, is consent for inclusion in bank needed or is a waiver of informed consent permissible?
  - If data/specimens obtain for prior research study, is inclusion in bank consistent with prior consent, if any?
  - If consent is to be obtained for bank, how specific should consent be about the types of research to be carried out?
  - Will “tiered consent” be sought?
  - What will be said about the confidentiality of the data/specimens? Will data/bank provides to recipient investigators be de-identified, identifiable, coded? Does HIPAA or GINA apply?
- Reminder: regulatory requirements establish the “floor” of protections – additional requirements can always be included to further protect the welfare and interests of research participants.



## *Uniting Rare Diseases*

### *Advancing Rare Disease Research: The Intersection of Patient Registries, Biospecimen Repositories and Clinical Data*

#### *Session V*

#### *Human Subjects: Bioethical & Legal Issues for Clinical Studies*

##### *Ethical and legal Issues/Government Regulations*

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##### *Human Subjects: Ethical & Legal Issues (45 CFR 46)*

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# Presumed goal

- Centralized infrastructure to support rare disease data registry that includes/or at least interacts with bio-specimen repository
- Must understand the basics

# The Basic Model



# The Basic Model



# Basic Concerns of the First Circle

- Someone must 'own' the repository/registry and be responsible for the:
  - Rules of operation
  - Addressing regulatory issues
  - Addressing ethical issues
  - Addressing business issues

# The Regulatory Issues

- When does 45 CFR 46 Apply?
- When does HIPAA apply?

# **When does 45 CFR 46 Apply?**

- **Apply to human subject research conducted or supported by U.S. Department of Health and Human Services**
- **If U.S. institution chooses to apply to all human subjects research through a Federalwide Assurance—apply regardless of source of support**

# Applicability of HHS Regulations

Research [45 CFR 46.102(d)]?

A light blue arrow pointing downwards from the 'Research' text to the 'Human subjects' text.

Human subjects [45 CFR 46.102(f)]?

A light blue arrow pointing downwards from the 'Human subjects' text to the 'Exempt' text.

Exempt [45 CFR 46.101(b)]?

# Applying 45 CFR 46 to a Research Registry (or Biospecimen Repository)



# Applying 45 CFR 46 to a Research Registry (or Biospecimen Repository)



## Research Registry Study

### Research?

- Yes

### Human subjects?

- Research intervention/interaction?  
(e.g. health data obtained for registry  
from research survey)
- Identifiable private information?  
(e.g. identifiable health information  
obtained from medical record)

# Applying 45 CFR 46 to a Research Registry (or Biospecimen Repository)



## Research Registry Study

### If Human Subjects Research:

- IRB review – at least one institution is “engaged.”
- Informed consent or waiver

# Applying 45 CFR 46 to a Research Registry (or Biospecimen Repository)

Data sources



Research  
Registry



Recipient Investigators

Plus:

- Are subjects children? Is child assent needed?
- Does HIPAA's or GINA's protections apply?

## Research Registry Study

### Informed consent considerations:

- If data obtained for clinical purposes, is consent for inclusion in bank needed or is a waiver permissible?
- If data obtained from prior research study, is inclusion in registry consistent with prior consent, if any? Is specific consent for inclusion in bank needed?
- If consent is to be obtained for registry, how specific should consent be about future research? Will "tiered" consent be an option?
- What will be said about confidentiality of data? Will registry provide investigators with de-identified, identifiable, or coded data? Under what conditions?

# HIPAA Issues

- There is no single answer
- Questions to ask:
  - Which components are covered by HIPAA?
    - The Registry itself?
    - Data source institutions
  - What data is involved?
    - Is it PHI (personal health information)
    - Is it identifiable?
    - Is it clinical PHI? Is it research PHI?

# More Issues

- Differences between informed consent and authorization
  - N.b., permission for broad future uses
- How to determine identifiability
- The logistics of consent
  - By whom?
  - When?
  - Where?

# The Basic Model



# Basic Concerns of the Second Circle

- Who is allowed to access data/material?
- Who makes that decision?
- Which regulations apply?
  - 45 CFR 46
  - HIPAA
- Are there other ethical issues that should be addressed?

# Applying 45 CFR part 46 to a Research Registry (or Biospecimen Repository)



## Research Study

**Research?**

- Yes

**Human subjects?**

- Identifiable private information?
- Coded?

# Applying 45 CFR part 46 to a Research Registry (or Biospecimen Repository)



## Research Study

### If human subjects research:

- IRB review—at least 1 institution is engaged
- Informed consent or waiver

# Applying 45 CFR part 46 to a Research Registry (or Biospecimen Repository)



## Research Study

### Informed consent considerations:

- Is currently proposed research consistent with prior consent, if any?
- Does prior consent fulfill informed consent requirements for the current study?
- If data obtained for registry when subject was a child, is consent needed from now-adult subject?

# **WHAT ABOUT FUTURE CONSENT?**

**Can original consent fulfill the informed consent requirements for a current study?**

- **Yes – if the prior informed consent meets the informed consent requirements of 45 CFR 46.116 for the current research study.**

**Note: HIPAA Authorization must be research study specific**

# Reminder

- **45 CFR 46 establish the federal “floor” for human subject protections**
- **Local law may create additional requirements (including international standards)**
- **Regulatory requirements do not address all relevant ethical considerations**

# Complexities of a centralized infrastructure

- What would the registry look like?
  - All data placed into a common-use bank?
  - Separate 'rooms' for separate diseases?
- Would every disease group agree on:
  - Types of data going into the bank?
    - Clinical vs research
  - Definition of identifiability?

# Complexities of a centralized infrastructure

Would every disease group support:

- A single governance structure?
- Rules for depositing and accessing
- Policies regarding:
  - Return of research results
  - Withdrawal of data upon request of subject/s
  - Etc.

# Complexities of a centralized infrastructure

- Who would be in charge?  
*(who 'goes to jail' for noncompliance)*
  - Single 'owner'
  - Committee
- Financial support
  - Equal commitment from all involved?
  - Sliding scale?

# Complexities of a centralized infrastructure

- What if:
  - A group wants to discontinue collaboration?
  - A new group wants to join?
  - The money runs out?

# OHRP RESOURCES

- 45 CFR part 46:

<http://www.dhhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>

- Human subject regulations decision charts:

<http://www.dhhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm>

- Repositories and databases:

<http://www.dhhs.gov/ohrp/humansubjects/guidance/reposit.htm>

- Coded guidance: <http://>

- Engagement:

<http://www.hhs.gov/ohrp/humansubjects/guidance/engage08.pdf>

- Informed consent FAQs:

<http://www.hhs.gov/ohrp/informconsfaq.html>