Presumed goal:
Centralized infrastructure to support rare disease data registry that includes/or at least interacts with bio-specimen repository.

Development requires understanding of basic banking construct:

It is easiest to consider the basic issues in the simplest situation – bank on a single site. As more sites are invited, the same questions must be addressed.

**The data/tissue source** – the regulatory oversight will vary as a function of specific characteristics, for example:
- Clinical vs research source
- Identifiability of the data/specimen
- Obtained with informed consent/authorization
  - If yes, is the banking the primary or secondary use
  - What did the consent include in terms of the down-stream uses? Sharing?
  - Who obtained consent? Banking personnel? Individual investigators?

**The bank itself** – specific characteristics that must be considered:
- Will the bank passively hold the data/specimens – or process them in some way; e.g., abstract DNA
- Will the bank maintain identifiable specimens/data? Or not?
- Who ‘owns’ the bank – who is responsible for the governance
- Rules of the bank:
  - For example, does the bank have any rules re: return of research results

**Data/tissue recipients** – for consideration
- Are there eligibility criteria for obtaining materials from the bank?
  - Any limitations? E.g., only those who deposit? Commercial entities?
- What can recipients obtain?
  - Data: identifiable? Aggregate only etc
  - Specimens: identifiable?
- Who determines if the recipient should get the material?
  - IRB approval required
Internal bank review?

- Return to the bank
  - Must recipients return research results to the bank for others to use?
- Can recipients return research results to individuals? If so, does the bank determine the process?

These are just examples of details that merit attention for a single bank.

What additional complexities would a centralized infrastructure introduce?

1. What materials: would different diseases have different requirements re:
   a. Clinical vs research materials
   b. Identifiability – and ability to up-date
   c. Type and handling of tissue
2. Could the various disease groups agree on:
   a. Governance of the repository/bank
   b. Rules for depositing and accessing materials
   c. Policies re: sharing – who can access?
   d. Policies re: return of research results?
3. Who would provide the funds?
   a. Equal commitment or sliding scale
4. Who would be in charge?
   a. Single owner? Versus committee
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
P. Pearl O’Rourke, MD
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Human Subjects: Ethical & Legal Issues (45 CFR 46)
Julie Kaneshiro
Policy Team Leader
Office for Human Research Protections
U.S. Department of Health and Human Services
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

Data sources → Research Registry → Recipient Investigators
The Basic Model

Data sources → Research Registry → Recipient Investigators
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)]?

Human subjects [45 CFR 46.102(f)]?

Exempt [45 CFR 46.101(b)]?
Applying 45 CFR 46 to a Research Registry (or Biospecimen Repository)

Data sources

Research Registry

Recipient Investigators

Research Registry Study

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

Research Registry Study

Data sources

Recipient Investigators

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)

Data sources ➔ Research Registry ➔ Recipient Investigators

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

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?

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

Data sources → Research Registry → Recipient Investigators
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)

Data sources

Research Registry

Recipient Investigators

Research Study

Research?
• Yes

Human subjects?
• Identifiable private information?
• Coded?
Applying 45 CFR part 46 to a Research Registry
(or Biospecimen Repository)

Data sources → Research Registry → Recipient Investigators

**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)

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/repositories.htm

- Coded guidance:  http://

- Engagement:  
  http://www.hhs.gov/ohrp/humansubjects/guidance/engage08.pdf

- Informed consent FAQs:  
  http://www.hhs.gov/ohrp/informedconsfaqs.html