

# **Establishing and Using Specimen and Data Repositories**

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# Objectives

- Review applicable regulations
- Identify methods to provide subject protection and address ethical issues in:
  - setting up specimen and data repositories
  - the collection, storage and distribution of specimens/data for research
- Identify and consider some of the more challenging issues in this area

# Overview of Presentation

- General banking issues/types of banks
- Applicable regulations
- Risks and risk assessment
- Methods for protecting subjects
- Data security
- Protocol content
- Consent Issues
- Access, dissemination, and other issues
- Challenging/unresolved issues
- Tools to help

# The “Simplest” Repository Model



Human Subjects?

IRB Review?

Informed Consent?

Privacy Rule require.?

State, local, instit. require.?

International regulations?

Ethical/responsible research

Human Subjects?

IRB Review?

Repository Policies

Privacy Rule require.?

State, local, instit. require.?

International regulations?

Ethical/responsible research

Human Subjects?

IRB Review?

Informed Consent?

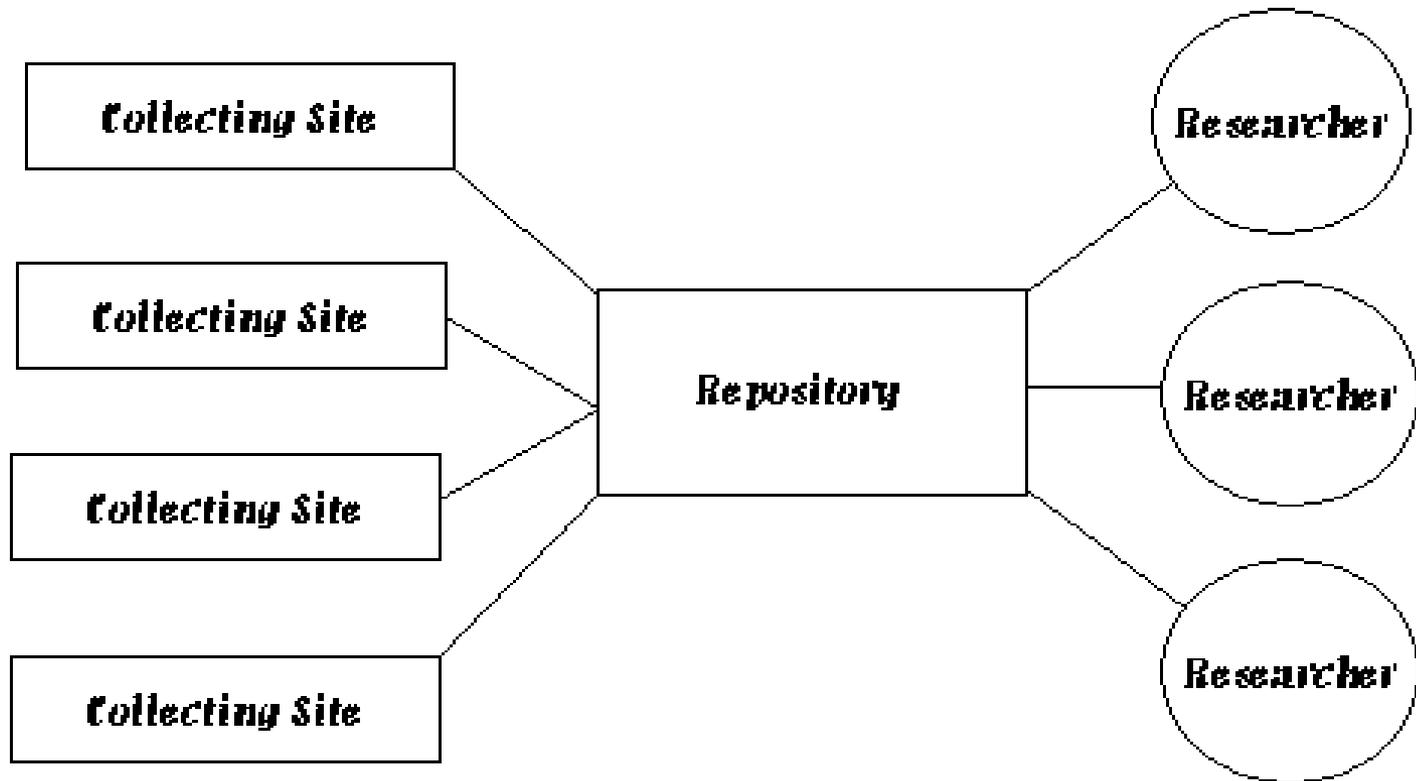
Privacy Rule Require.?

State, local, instit. require.?

International regulations?

Ethical/responsible research

# A More Complex Model



# Types of banks/repositories

Type of Bank	Specimens	Subject Data
Traditional Bank	Stored Centrally	Stored Centrally
Procurement	Collected to meet need	Limited data
Virtual	Stored at multiple collecting institutions	Stored centrally
Fully virtual/distributed (e.g. caBIG)	Stored at multiple collecting institutions	Stored at multiple collecting institutions

# Overview of Applicable Regulations/Policies

How Does 45 CFR Part 46  
Apply to Research  
Repositories and  
Databases?

# Definition of a Human Subject: 45 CFR part 46

## Human Subject

A living individual about whom an investigator conducting research obtains:

(1) Data through intervention or interaction with the individual; or

(2) Identifiable private information

[45 CFR 46.102(f)] [45 CFR 46.102(f)]

# Research Repositories & Databases

## 3 Paths to Human Subjects Research

- Creating a research repository/database ***through intervention or interaction with individual***
- Creating a research repository/database ***by obtaining identifiable private information***
- Obtaining identifiable private information ***from a research repository/database.***

*(Slide courtesy of J. Kaneshiro, OHRP)*

# OHRP Guidance on Coded Private Information or Biological Specimens

- “Guidance on Research Involving Coded Private Information or Biological Specimens”
  - Defines when research involving data or specimens does not involve human subjects
- <http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf>

# OHRP Guidance on Coded Private Information or Biological Specimens

## Definition of “Coded”:

(1) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and

(2) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

# OHRP Guidance on Coded Private Information or Biological Specimens

*“In general, OHRP considers private information or specimens to be individually identifiable as defined at 45 CFR 46.102(f) when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.”*

However, the OHRP coded specimens policy allows exceptions under certain conditions.

# OHRP Guidance on Coded Private Information or Biological Specimens

*“Conversely OHRP considers private information or specimens not to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly through coding systems.”*

# OHRP Guidance on Coded Private Information or Biological Specimens

Research involving only coded information or specimens is not considered to involve human subjects if the following conditions are both met:

- (1) the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; **AND**
- (2) the investigator(s) cannot readily ascertain the identify of the individual(s) to whom the coded private information or specimens pertain.

# OHRP Guidance on Coded Private Information or Biological Specimens

Examples of When Coded Data/Biologic Specimens Are Not Individually Identifiable to Investigators:

- (a) the key to decipher the code is destroyed before the research begins;
- (b) the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased

# OHRP Guidance on Coded Private Information or Biological Specimens

## Examples of When Coded Data/Biologic Specimens Are Not Individually Identifiable to Investigators:

(c) there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or

(d) there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

# OHRP Guidance on Coded Private Information or Biological Specimens

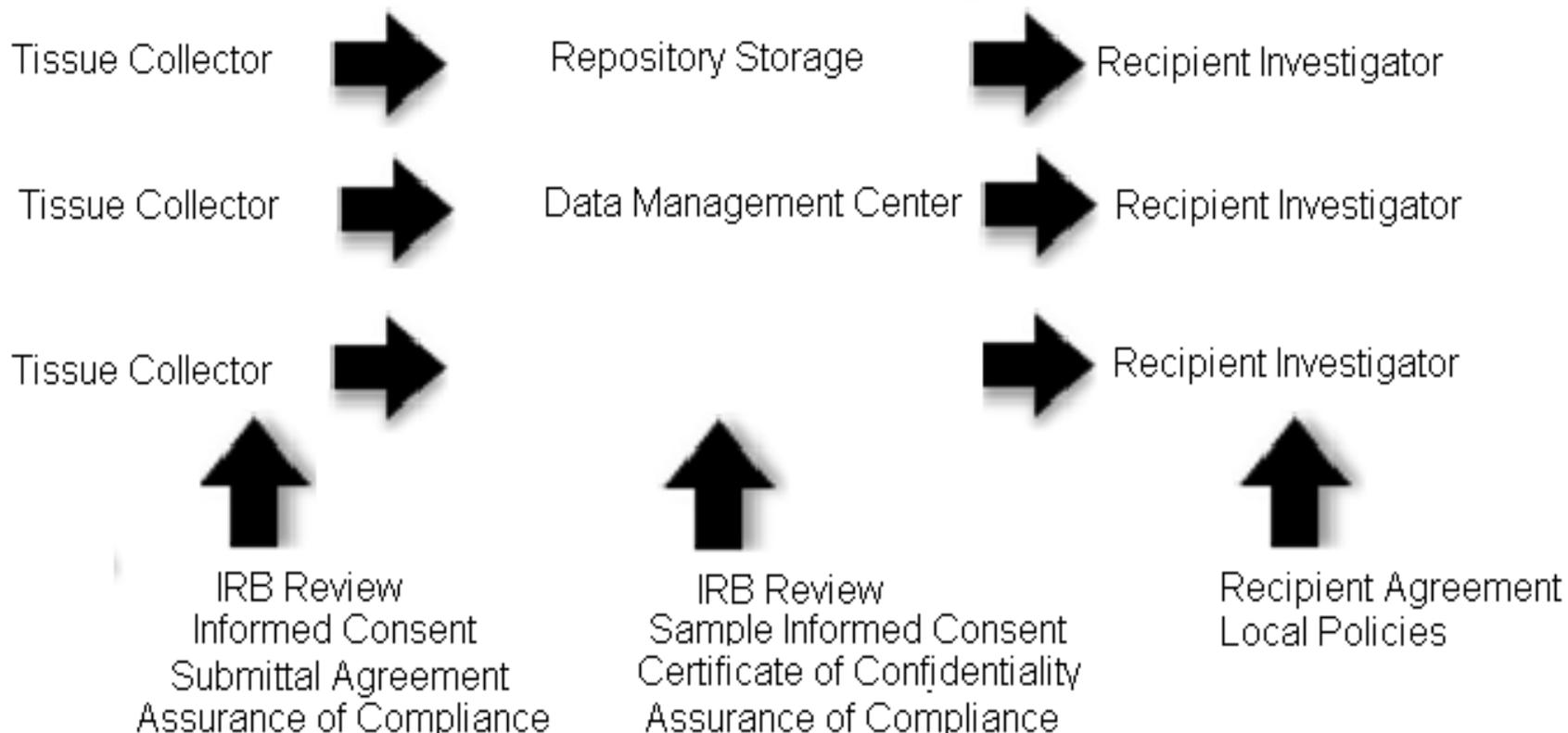
## Only applies if:

1. Person(s) doing coding of data/specimens and person(s) holding codes are not part of the research team; **AND**
2. Specimens/data are not being obtained for the specific research in question by an interaction or intervention with living individuals.

Issues to Consider in the Research Use of Stored Data or Tissues  
OFFICE FOR PROTECTION FROM RESEARCH RISKS

November 7, 1997

Human Tissue Repositories collect, store and distribute human tissue materials for research purposes. Repository activities involve three components: (i) the collectors of tissue samples; (ii) the repository storage and data management center; and (iii) the recipient investigators. If supported by the Department of Health and Human Services (HHS), each component must satisfy certain regulatory requirements.



# How do the FDA Regulations Apply?

# How Do the FDA Human Subjects Regulations Apply?

- 21 CFR Part 50: Informed consent
- 21 CFR Part 56: IRB review
- 21 CFR Part 812: Investigational Device Exemption (IDE)
- Apply to all clinical investigations regulated by FDA
  - Biomedical research involving an unapproved drug, device or biologic and certain studies of approved products

# FDA Definition of a Human Subject

- **FDA**

- Human who participates in research either as a recipient of the test article or as a control. A healthy human or a patient. (21 CFR 50.3(g) and 56.102(e))
- Subject is an individual on whom or **on whose specimen** an investigational device is used. (21 CFR part 812)

# FDA Requirements for Informed Consent

- FDA exemptions to the requirement for informed consent are limited to emergency, life threatening situations, military operations
  - May pose challenges for some studies involving human specimens (e.g. development of assays using archived specimens)

# FDA Guidance

- FDA to exercise enforcement discretion, ***under certain circumstances***, with respect to requiring informed consent when human specimens are used in FDA-regulated in-vitro diagnostic device investigations
  - “Guidance on Informed Consent for *In Vitro* Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable”
  - <http://www.fda.gov/cdrh/oivd/guidance/1588.html>

# How Does the HIPAA Privacy Rule Apply?

# Use or Disclosure of PHI for Research Repositories

- Two separate activities to consider:
  - Use or disclosure of data to create the research or repository database
  - Subsequent use or disclosure of data in the database for a particular research protocol

# Use or Disclosure of PHI to Create the Research Repository or Database

- With an individual's Authorization
  - to create or maintain a research repository or database, no expiration required
- Authorization NOT required if one of the following applies:
  - IRB or Privacy Board waiver
  - Preparatory to research (with certain representations)
  - Limited data set (with data use agreement)
  - De-identified dataset
  - Research solely on decedents (with certain representations and documentation)
  - IC, waiver of IC, or express legal permission prior to compliance date (and other conditions of transition provisions met)

# Subsequent Use or Disclosure of PHI From Repository for Research

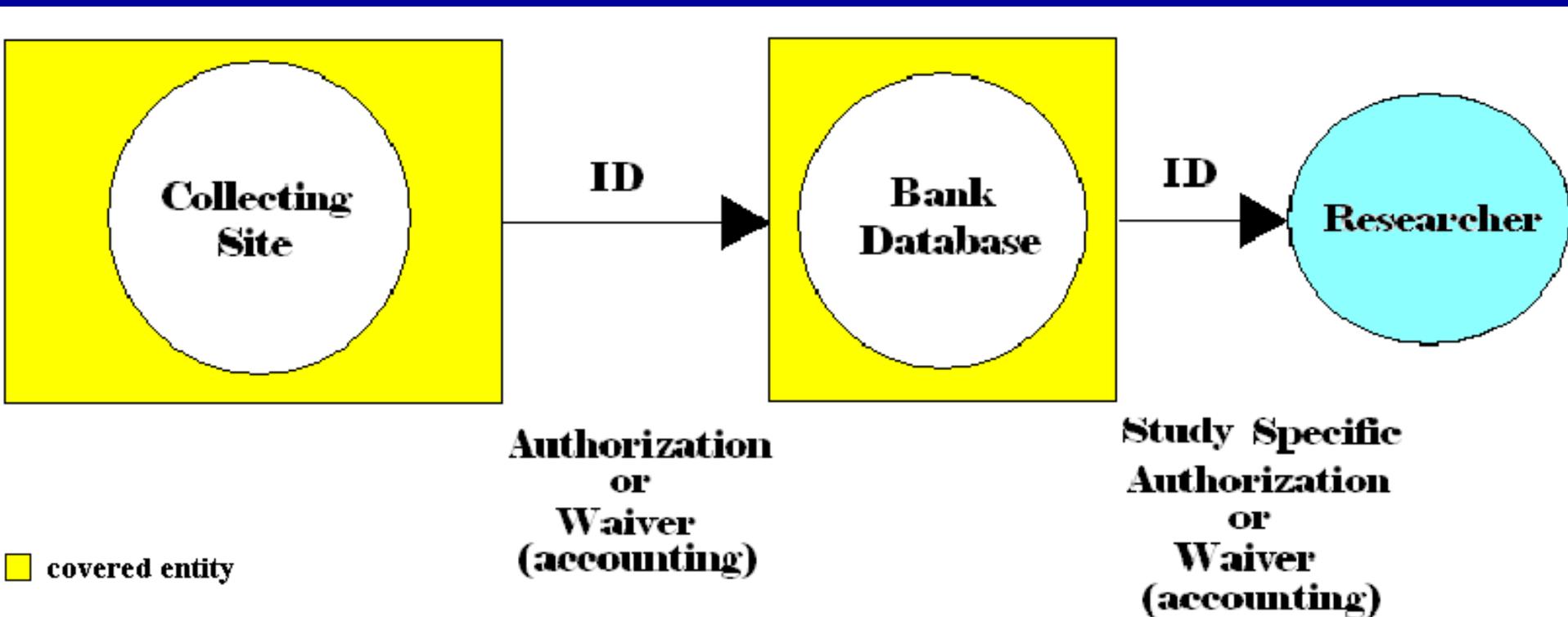
- With Individual's Authorization for research
  - Specific and meaningful
- Authorization NOT required if one of the following applies:
  - IRB or Privacy Board waiver
  - Preparatory to research (with certain representations)
  - Limited data set (with data use agreement)
  - De-identified dataset
  - Research solely on decedents (with certain representations and documentation)
  - IC, waiver of IC, or express legal permission prior to compliance date (and other conditions of transition provisions met)

# When the specific research is unknown at the time the data are collected

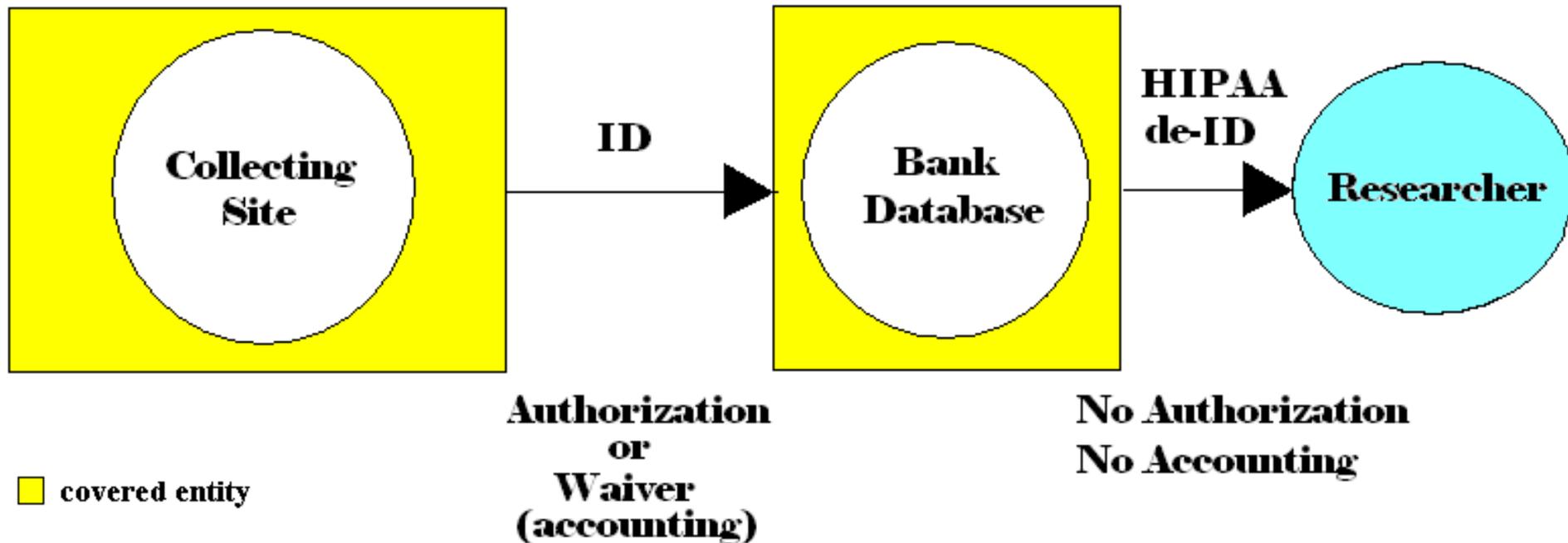
## Key points to remember:

- Authorization must be specific for the research use and disclosure of PHI from repositories, but authorization may be obtained to create and maintain a research repository
- Authorization is NOT required for the subsequent use or disclosure from the repository of de-identified data or a limited dataset pursuant to a data use agreement

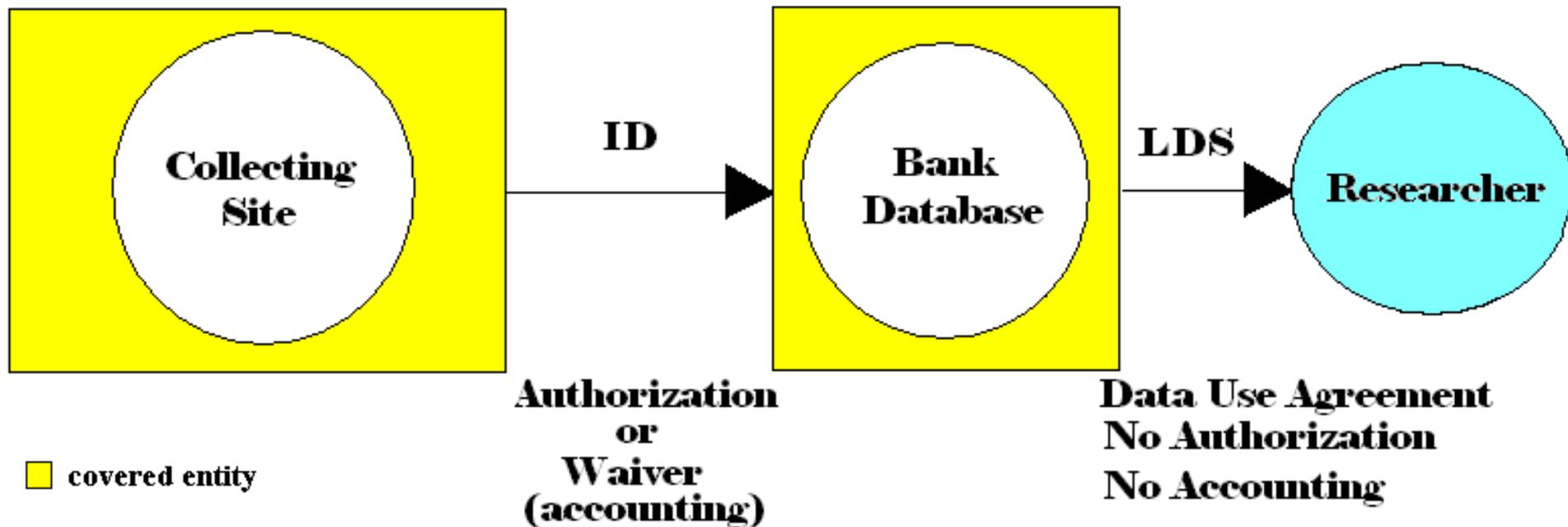
# Model 1



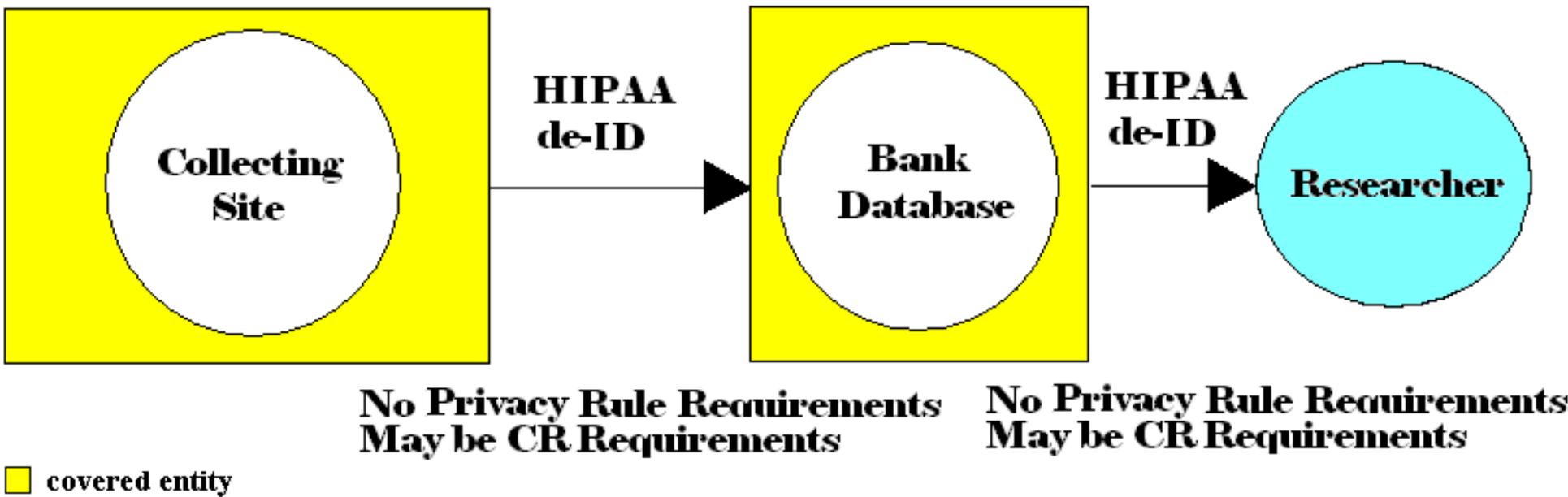
# Model 2



# Model 3



# Model 4



# Risks and Risk Assessment

How do you assess risk for research involving human specimens and data?

When is research using human specimens and data greater than minimal risk?

# Risks

- Physical risks
- Psychosocial risks
  - Anxiety
  - Loss of privacy of personal information/research data
    - Loss of employment or insurability
- Risks associated with unvalidated research data
- Group harms

# Assessment of Level of Risk

- Risk assessment critical to determine if waiver of informed consent is appropriate
- National Bioethics Advisory Commission<sup>1</sup> recognized that specimen research may be considered minimal risk if it:
  - protects confidentiality
  - protects privacy
  - includes plan for **whether and how** to reveal findings to the subject

<sup>1</sup> Research Involving Human Biological Materials: Ethical Issues and Policy Guidance , 1999

# Assessment of Privacy Risks

- Identifiability
- Sensitivity of identifiable data
- Nature of the research
- Likelihood of disclosure of research or subject information
  - Systems and policies in place to protect privacy and confidentiality
- Assessment should be based on probability and magnitude of harm

# Repository Subject Protections: Multiple Levels of IRB Review

- Review of repository operating procedures and policies
- Review of individual research protocols for use of identifiable specimens and data

# Repository Subject Protections: Policies, Governance and Oversight

- Operating policies and procedures
  - Procedures for obtaining informed consent
  - Procedures for protecting privacy/confidentiality; access to specimens/data
  - Policies and procedures for return of research results (if and under what conditions)
- Governance and oversight
  - Steering and/or oversight committees, ethics advisory boards

# Repository Subject Protections: Privacy/Confidentiality Procedures

- Anonymization of specimens/data
- Coding of specimens/data
  - Links maintained by repository but identifying information never released to investigators
- Encryption
- Limited access/secure storage
- “Honest Broker” systems
- Certificates of Confidentiality (where appropriate)

# Repository Subject Protections: Privacy/Confidentiality Procedures

## Employee confidentiality agreements

“I understand that in my role as an employee of the XYZ Tissue Bank, I may have access to confidential information such as patient names or patient-identifying information, patient demographics, medical records, etc. I understand that my access to this information is strictly for the purposes of carrying out my employee responsibilities and that any disclosure to third parties or other misuse of this confidential information is strictly prohibited. A breach of confidentiality may result in the termination of my employment with the XYZ Tissue Bank.”

# Repository Subject Protections: Investigator User Agreements

- Address:
  - Use of specimens/data
  - Human subjects protections
  - Sharing of specimens with third parties
  - Commercial use of specimens
  - Biohazards
  - Indemnification

# Data Security

# Data Security

- Institutional and HIRPP policies and procedures
- HIPAA Security Rule
  - <http://www.cms.hhs.gov/SecurityStandard/>
- Good Practice
  - Coding, encryption, and secure physical and electronic storage of sensitive information
  - Collect and store only that information needed for the purposes of the research
  - Restrict physical and electronic access to only those with need to know

# Data Security

- Good Practice
  - Separate identifying information from research data
  - Destroy data when no longer needed according to institutional policies and relevant regulations
  - Don't store sensitive information on portable electronic devices (laptops, thumb drives, or other portable media)
  - Transmit sensitive information only when encrypted

# Data Security

- Good Practice
  - Involve IT experts upfront in design of data repositories and operating procedures
  - Review data storage and transmission procedures with IT experts on regular basis
- Information Resources:
  - National Institute of Standards and Technology Special Publications
    - <http://csrc.nist.gov/publications/PubsSPs.html>
  - Center for Internet Security
    - <http://www.cisecurity.org/>

# Informed Consent

- Informed consent required when there is intervention/interaction with a living individual or private identifiable information is being collected and/or used, unless waived by the IRB
- Should be clear and understandable

# Additional Informed Consent Content

- Must meet requirements of human subjects regulations
- In addition, should also include:
  - Description of specimens/data and process used for collecting them
  - Risks, including risks to privacy and confidentiality, and methods to protect risks
  - Description of the purpose of the collection and conditions for sharing
  - Types of research to be conducted

# Additional Informed Consent Content

- Statement of the right to withdraw
- Whether results will be returned
- Plans for re-contact, if any
- As appropriate:
  - Information on the consequences of DNA typing
  - What will happen to specimens/data when no longer useful, when repository loses support, or is transferred to others
  - Details about where the specimens will be stored (particularly relevant for international research)
  - Use of “tiered” consent

# Consent for Collections Established from Existing Specimens/Data

- Is use consistent with initial consent under which specimens/data were collected?
- If not, can informed consent be waived:
  - no more than minimal risk to the subjects;
  - the waiver will not adversely affect the rights and welfare of the subjects;
  - the research could not practicably be carried out without the waiver; and
  - *whenever appropriate*, the subjects will be provided with additional pertinent information after participation.
- Is new consent required?

# Specimen/Data Access and Dissemination

- Procedures for determining that research use is scientifically appropriate and consistent with consent
- Procedures for prioritizing requests for access
- Systems in place to reduce risk of harms to groups
- Specimens/data distributed without identifiers
- Receipt of documentation of IRB approval from recipient investigators (where appropriate)
- Compliance with HIPAA Privacy Rule, where applicable

# Other Issues

- Financial Issues
  - Reasonable cost recovery generally appropriate
- Tracking
  - Systems to document location, distribution and use of specimens/data
  - Systems to track the types of research for which consent was given

# Other Issues

- Resource Sharing/IP Considerations
  - Material Transfer Agreements specify the rights and obligations of both the provider and the recipient, including any IP terms and publication rights consistent with NIH Research Tools Policy
- Benefit Sharing
  - Annual reports, newsletters, summaries of general research findings
  - Technology transfer

What needs to be in the  
protocol submitted to the  
IRB?

# Points to Consider: Information to Include in a Repository Protocol for IRB Review

- Name, purpose, and overall goals of repository
- Administration and oversight of repository
  - Who is responsible; oversight mechanisms in place
- Procedures for specimen and data collection
  - Identification of subjects or previously existing specimens; study populations
  - Information collected with the specimen, especially identifiers
  - Ongoing subject interactions, if any

# Points to Consider: Information to Include in a Repository Protocol for IRB Review

- Recruitment and Informed Consent
  - Who, how and when
  - Consent process and form
  - If waiver is requested, justification
  - Plans for obtaining consent when a child reaches age of consent for research; or request for waiver
  - Procedure for subjects to withdraw their consent and what will be done with specimens/data

# Points to Consider: Information to Include in a Repository Protocol for IRB Review

- Specimen and Data Storage/Retention
  - Linkage to subject identities, if any
  - Who will have access to identifying information?
  - How will specimens/data be coded?
  - Procedures for secure storage
  - How long will specimens/data be retained?
- Specimen derivation and processing
  - Cell lines, DNA/RNA, etc.

# Points to Consider: Information to Include in a Repository Protocol for IRB Review

- Specimen and Data Distribution
  - What specimens and data will be provided?
  - Processes in place for assuring appropriate access
  - Policy regarding secondary distribution
  - Investigator usage agreements/MTAs
  - Policy regarding commercial use

# Points to Consider: Information to Include in a Repository Protocol for IRB Review

- Protection of subject autonomy, privacy, confidentiality
  - Who has access to identifiers and keycode
  - Policies and procedures in place to protect subjects
  - Policy regarding release of personal identifiers
  - Policies for assuring uses are consistent with consent
  - How will repository comply with HIPAA Privacy Rule

# Points to Consider: Information to Include in a Repository Protocol for IRB Review

- Return of Research Results
  - Policy regarding when, if ever, individual research results will be returned to subjects
  - Policy regarding return of aggregate, generalized research findings
- Other Issues
  - Plans if PI leaves institution or repository loses financial support

# Challenging/Unresolved Issues

# Return of Research Results

- When should individual research results be returned to subjects?
  - Tension between perspectives on the rights of individuals to information about themselves vs. harms associated with inappropriate return of research results
- Harms associated with return of individual results that have not been clinically validated or are of unknown clinical significance
  - Stress, anxiety, and even physical harms if used inappropriately for medical decision making

# Return of Research Results

- Clinical Laboratory Improvement Amendments (CLIA) 1988
  - Prohibits return of results for clinical care if tests not performed in CLIA approved labs
- Informed consent should address if and under what circumstances individual results will be returned to subjects
- May be appropriate to provide **generalized, aggregate** research findings to subjects

# Unresolved Issue: Ownership/Control of Samples

- Moore v. Regents of the University of California
- Greenberg et al. v. Miami Children's Hospital
- Catalona v. Washington University
- Havasupai Case

# Custodianship

- Different from ownership
- “Caretaking responsibility”<sup>1</sup>
  - Governance, management and oversight
  - Conditions for access and use
  - Documented plans for disposition of specimens and data
    - Plans if repository/bank closes
    - Plans for transfer if PI leaves institution

<sup>1</sup>(NCI Best Practices for Biospecimen Resources, June 2007)

# Tools to Help (See also Handouts)

- Clinical Research Policy Analysis and Coordination Program (CRpac)
  - <http://www.crpac.od.nih.gov>
- Public Responsibility in Medicine and Research (PRIM&R) Human Tissue/Specimen Banking Working Group Report
  - <http://www.primr.org>
- NCI Model Consent
  - <http://www.cancerdiagnosis.nci.nih.gov/specimens/legal.htm#3b>

# Best Practices

- **International Society for Biological and Environmental Repositories (ISBER) Best Practices For Repositories: Collection, Storage, Retrieval and Distribution of Biological Materials for Research**
  - *Cell Preservation Technology, March 2008 issue;*  
<http://www.isber.org/ibc.html>
- **NCI Best Practices for Biospecimen Resource**
  - [http://biospecimens.cancer.gov/global/pdfs/NCI\\_Best\\_Practices\\_060507.pdf](http://biospecimens.cancer.gov/global/pdfs/NCI_Best_Practices_060507.pdf)

# Acknowledgements

- Sharon Friend, UCSF

*“Achieving Excellence in DOD Human Research Protection Programs: Taking An Active Role”  
Training Conference, June 26 – 27, 2008  
“Establishing and Using Specimen and Data Repositories”  
Marianna Bledsoe, M.A.  
Clinical Research Policy Analysis and Coordination Program, OBA, OSP, NIH*

**Regulations and Policy Documents Related to the Research Use of Human Specimens and Data**

US Regulations

- HHS Human Subjects Regulations:  
45 CFR part 46  
<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>
- FDA Human Subjects Regulations:  
21 CFR parts 50, 56, 812  
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>
- HIPAA Privacy Rule: Final Modification, 45 CFR Parts 160 and 164, “Standards for Privacy of Individually Identifiable Health Information, Final Rule”, August 14, 2002  
<http://www.hhs.gov/ocr/hipaa/privrulepd.pdf>
- HIPAA Security Rule (45 CFR parts 160, 162, 164)  
<http://www.hhs.gov/ocr/hipaa/>
- Privacy Act of 1974, 5 U.S.C. § 552a  
[http://www.usdoj.gov/oip/04\\_7\\_1.html](http://www.usdoj.gov/oip/04_7_1.html)

Policy and Educational Documents:

OHRP Policy Documents:

- OHRP: Issues to Consider in the Research Use of Stored Data or Tissues, guidance memorandum issued in November 1997  
<http://www.hhs.gov/ohrp/humansubjects/guidance/reposit.htm>
- OHRP: Engagement of Institutions in Research, guidance memorandum issued January 26, 1999  
<http://www.hhs.gov/ohrp/humansubjects/assurance/engage.htm>
- OHRP: Guidance on Research Involving Coded Private Information or Biological Specimens, issued August 10, 2004  
<http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf>

FDA Guidance Documents:

- FDA Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens That are Not Individually Identifiable  
<http://www.fda.gov/cdrh/oivd/guidance/1588.pdf>

NIH Documents:

The NIH has a website with a number of educational documents on the Privacy Rule and research (<http://privacyruleandresearch.nih.gov/>), including the following:

- NIH: Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule (issued April 14, 2003; revised 7/13/04)  
[http://privacyruleandresearch.nih.gov/pr\\_02.asp](http://privacyruleandresearch.nih.gov/pr_02.asp)
- NIH: Research Repositories, Databases and the HIPAA Privacy Rule issued July 2, 2004  
[http://privacyruleandresearch.nih.gov/research\\_repositories.asp](http://privacyruleandresearch.nih.gov/research_repositories.asp)
- NIH: Institutional Review Boards and the HIPAA Privacy Rule, issued July 8, 2004  
<http://privacyruleandresearch.nih.gov/irbandprivacyrule.asp>

International Human Research Protections:

- International Compilation of Human Research Protections  
<http://www.hhs.gov/ohrp/international/HSPCompilation.pdf>

*“Achieving Excellence in DOD Human Research Protection Programs: Taking An Active Role”  
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“Establishing and Using Specimen and Data Repositories”  
Marianna Bledsoe, M.A.  
Clinical Research Policy Analysis and Coordination Program, OBA, OSP, NIH*

**Useful Resources and Tools Related to Human Specimen and Data Repositories**

- **Clinical Research Policy Analysis and Coordination Program (CRpac) website**
  - [http://crpac.od.nih.gov/issue\\_Human\\_Tissues\\_Data.asp](http://crpac.od.nih.gov/issue_Human_Tissues_Data.asp)
  - Includes links to pertinent resources, policies and regulations
  
- **Report of the Public Responsibility in Medicine and Research (PRIM&R) Human Tissue/Specimen Banking Working Group**
  - <http://www.primr.org/PublicPolicy.aspx?id=68>
  - This report, written by a group representing the full range of stakeholders in specimen research, is organized into two parts. The first part includes a discussion of current challenges in the area of human specimen banking and recommendations to the federal regulatory and funding agencies. The second part provides tools for IRBs, repository managers, and researchers in the form of educational materials, discussions of relevant issues, and points to consider
  
- **National Cancer Institute, Cancer Diagnosis Program, 50-State Survey of Laws Regulating the Collection, Storage, and Use of Human Tissue Specimens and Associated Data for Research**
  - <http://www.cancerdiagnosis.nci.nih.gov/pdf/50StateSurvey.pdf>
  
- **National Cancer Institute/National Action Plan on Breast Cancer Model Informed Consent and Patient Brochure**
  - <http://www.cancerdiagnosis.nci.nih.gov/specimens/legal.htm>
  
- **NCI Tissue Brochure, “Providing Tissue for Research: What You Need to Know”**
  - <http://www.cancer.gov/clinicaltrials/resources/providing-tissue.pdf>
  - Patient educational brochure

For further information contact:

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