

**Report of the Public Responsibility in Medicine and
Research (PRIM&R) Human Tissue/Specimen
Banking Working Group**

Part I Assessment and Recommendations

March 2007

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FOREWARD

This White Paper was written by the Public Responsibility in Medicine and Research (PRIM&R) Human Tissue/Specimen Banking Working Group to address some of the considerable legal, ethical and policy challenges related to the collection, storage, distribution and use of human specimens and associated data for research. The idea emanated from an initial meeting of interested individuals at the 2003 Annual Meeting of PRIM&R in Washington DC in December, 2003 including Marianna Bledsoe, Julie Kaneshiro, Susan Kornetsky, Pearl O'Rourke, Joan Porter, Joan Rachlin, Susan Rose, and Ada Sue Selwitz. As a result of those discussions, we launched an effort to evaluate some of the legal and ethical issues related to specimen banking and consider how they might be addressed. This effort involved a two-pronged approach. The first consisted of a full day program of presentations and discussion of the issues at the PRIM&R sponsored meeting, "Conflicts of Interest, Privacy/Confidentiality, and Tissue Repositories: Protections, Policies, and Practical Strategies" in Boston, Massachusetts in May, 2004 and the second involved the establishment of a working group of stakeholders, the PRIM&R Human Tissue/Specimen Banking Working Group.

The establishment of the PRIM&R Human Tissue/Specimen Banking Working Group and the development of this White Paper was a collaborative effort between PRIM&R, Partners HealthCare Systems Inc., the NIH Clinical Research Policy Analysis and Coordination Program and the Cancer Diagnosis Program, NCI. The purpose of the Working Group was to identify current barriers to the collection, storage, distribution, and use of human specimens and data in research and strategies for overcoming those barriers while protecting subjects. The Working Group reflected the full range of stakeholders involved in specimen banking (see attached participant list) and included Institutional Review Board members, lawyers, ethicists, researchers and repository managers, patient advocates, and representatives from industry, academia and government. The Group held a series of face-to-face meetings, conference calls and e-mail discussions beginning in May 2004 to identify and deliberate on the many complex legal, ethical and policy issues related to the specimen banking and use, culminating in the current White Paper.

The White Paper includes recommendations to the Federal regulatory and funding agencies as well as tools for IRBs, repository managers and researchers in the form of educational materials and discussions of relevant issues and points to consider. The White Paper does not represent official policy guidance, although official policy is cited as such in the appropriate sections of the document. The Working Group included individuals from federal regulatory and funding agencies and departments only in an ex-officio capacity. Every effort was made to provide current and accurate agency policies. However, this document does not constitute official policy guidance. The recommendations in this document are based on discussions in the Tissue Working Group and do not represent the official position of any participating agency and department. The Working Group also strongly urges that when and if guidance and rules are revised or modified by federal agencies, robust consultation with the user community be included in the process.

While it was not possible to provide a complete discussion of all of the complex and evolving issues related to specimen banking in this document, the Working Group believes that it will be valuable to federal regulatory and funding agencies, IRBs, researchers and repository managers and their institutions. Comments and questions about the Paper should be directed to Pearl O'Rourke at: info@primr.org

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INTRODUCTION

Human blood, specimens, DNA, and other human biological materials (human specimens) are increasingly valuable resources in medical research. Studies using human specimens include, for example, investigations of how normal and diseased cells work, examinations of the cellular differences between people who do or do not respond to a particular drug, and research into the genetic basis of disease. Human specimens and associated data provide critical resources for basic scientific discoveries and for translating those discoveries into improved medical care. They have become invaluable in supporting emerging technologies that focus on causes of human diseases, in the discovery of predictors of development and course of disease, and in the development of new therapies. In addition, sophisticated information technology has the potential to make an unprecedented amount of accompanying clinical data available for research using human specimens, which will accelerate the pace of discovery. Although these developments offer great promise, the power of these molecular and informatics technologies has heightened concerns about privacy and confidentiality and the need to protect the rights and welfare of persons from whom specimens and data are obtained. Thus, ensuring the public's trust is essential to guaranteeing the research community's continued access to human specimens.

Federal regulations governing research on human subjects aim to protect the rights and welfare of individuals participating in research and serve to promote public trust, but these regulations were drafted well before the dramatic increase in the use of human specimens and data for research. In addition, the regulations were promulgated by different agencies to achieve different statutory and regulatory purposes and they differ widely in scope, terminology, and provisions. Moreover, although federal regulatory agencies have developed guidance documents to address many aspects of collection, storage, distribution and use of specimens and data for research, there is no single comprehensive guidance that covers the full spectrum of these activities. As a result, neither the regulations nor the regulatory guidance documents directly address many issues related to the use of specimens and data. In addition, overlapping and sometimes inconsistent regulations and a lack of clear regulatory language and comprehensive guidance have led to considerable confusion for researchers, repository managers, and Institutional Review Boards (IRBs). Finally, certain provisions of the existing regulations pose significant barriers to research using human specimens and data while offering little additional protection for the individuals from whom the specimens were obtained.

Purpose and Scope

The purpose of this white paper is to describe some of the major legal, ethical, and policy barriers related to the collection, storage, distribution and use of human specimens intended for research and to suggest some strategies—both short-term and long-term—for overcoming them. The short-term strategy is to provide tools to help IRBs, researchers, and repository managers understand the requirements of the various regulations and provide some reasonable approaches to meet those requirements (see section II). The longer-term strategy involves recommendations to federal regulatory and funding agencies that, if implemented, will clarify and facilitate research using human specimens and accompanying data while protecting the subjects from whom the specimens and data are obtained.

This paper was written by a working group of stakeholders interested in advancing biomedical research in the name of human health and in clarifying the opportunities and challenges raised by the research use of human specimens. It is not the first group to tackle this issue. In 1999, the National Bioethics Advisory Commission (NBAC) issued its report, *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance* (NBAC, 1999).¹ The discussion was further advanced by a response to the NBAC report issued by the Department of Health and Human Services (DHHS) in 2001.² While these earlier reports do not represent official policy guidance and have no regulatory status, they do present a comprehensive discussion of the various issues related to the use of human specimens in research.

This paper does not aim to duplicate these previous efforts, but rather to build on them by focusing more specifically on the issues and providing useful information for investigators, IRBs, repository managers and institutions that collect, store, and use human specimens and accompanying health information in research. Finally, the paper does not address the clinical use of human specimens in transplantation, transfusion, and organ donation, nor does it address the many ethical issues related to use of stem cells. While research databanks share many issues with human specimen banks, the focus here is on the use of human specimens and associated clinical data in research.

BACKGROUND

Human specimens are collected from individuals with specific diseases as well as healthy volunteers and encompass a wide range of samples, including solid specimens; body fluids, such as blood, saliva, and urine; and cells, such as cheek swabs. In addition, clinical data are often collected and maintained with the specimens, for example, the individual's diagnosis, drug regimens, and outcome. When the individual who provided the specimen or accompanying data is identifiable, concerns arise with regard to subject privacy and confidentiality.

Specimens and associated health information can be collected prospectively or obtained from existing archives: they can be collected specifically for research purposes or obtained during the course of routine medical care (e.g., residual material remaining after the removal of a tumor). Some specimen archives were created years ago. In many cases, these archives contain unique research specimens that would be impossible to replicate today because of changes in medical practice. Numerous scientific and medical advances have been made possible because of the availability of human specimens and data for research.³ While it is possible to learn a great deal from research using animal models, human materials are necessary to ensure that data derived from animal models are relevant to human disease.

¹Research Involving Human Biological Material:Ethical Issues and Policy Guidance. Volume I: Report and Recommendations of the National Bioethics Advisory Commission, August 1999, Volume II: Commissioned Papers, January 2000. (<http://www.georgetown.edu/research/nrcbl/nbac/pubs.html>)

² DHHS response to the NBAC report issued by the Department of Health and Human Services (DHHS) in 2001. (<http://aspe.hhs.gov/sp/hbm/report.htm>)

³ Korn, David, Contribution of the Human Tissue Archive to the Advancement of Medical Knowledge and the Public Health. Section E, Pages 1-30. *Research Involving Human Biological Material:Ethical Issues and Policy Guidance*. National Bioethics Advisory Commission. Volume II, Commissioned papers. January 2000.

The major benefits of research using human specimens and data are to the public health, that is, to society. In contrast, it is less likely that individual subjects will receive direct benefits from research conducted on their specimens and associated data. There may, however, be psychosocial benefits, such as a sense of empowerment and a feeling of having made a valuable contribution to society by facilitating scientific progress and medical research. While potential physical risks may be associated with the procedures used to obtain human specimens for research purposes (e.g., extra blood draw or biopsy); the predominant risks from subsequent research use are more likely to be psychosocial, primarily loss of privacy and/or confidentiality of private health information. These harms can occur if materials are used without permission or if personal health information associated with the human specimens falls into the hands of third parties who do not respect the rights and welfare of the research subject. These non-physical risks raise a variety of legal and ethical issues related to the use of human specimens and associated data, and their mitigation requires the involvement of a variety of stakeholders, including the subjects, researchers, government research and regulatory agencies, academia, industry, the medical community, and society at large.

To ensure the continued support of research using human specimens it is critical to establish appropriate practices and protections for individuals and institutions collecting, banking, and using these human specimens for research purposes. However, establishing standard best practices to address the legal, ethical and policy issues relevant to human specimen research is not easily achieved because of the heterogeneity of specimens collected and stored, differences in the reasons for their collection and storage (e.g., research use versus clinical care), and the wide variety of banking policies and procedures. Regulatory challenges include inconsistency and lack of clarity in federal regulations governing the use of human specimens and health information in research. This is compounded by vague and sometimes conflicting interpretations of policy by the regulatory agencies.

Stakeholders

One of the major challenges in addressing the legal, ethical, and policy issues related to research using human specimens and accompanying data is balancing the interests of the wide variety of stakeholders.

Researchers and repository managers are important stakeholders. In addition to the traditional pathology collections and specimen banks created by academic and not-for-profit research institutions, for-profit companies have established banks of specimens that are provided on a fee-for-service basis or through contractual arrangements with other companies.

The Federal Government is also a key stakeholder. Some federal agencies regulate human specimen banking for research purposes as well as research using those specimens. Applicable regulations include: the Federal Policy for the Protection of Human Subjects (codified by the Department of Health and Human Services (DHHS) at 45 CFR 46, and known widely as the “Common Rule”); Food and Drug Administration (FDA) regulations (21 CFR parts 50, 56, and 812); and the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA) (45 CFR part 160, & Subparts A & E of part 164). Both the Common Rule and FDA human subject regulations contain the central requirement for independent ethics review by an IRB and

for obtaining informed consent (except when that requirement can be waived under the Common Rule provision).

The federal Office for Human Research Protections (OHRP) is responsible for interpreting and providing guidance on HHS codification of the Common Rule for HHS conducted or funded human subjects research. Other federal departments and agencies conduct or fund research involving the collection, storage and distribution of human specimens and data (National Institutes of Health, Department of Veterans Affairs, Department of Defense, Department of Energy and others). These Departments and agencies have additional policies beyond the Common Rule and FDA regulations that apply to research they conduct or support. The DHHS Office of Civil Rights (OCR) is responsible for interpreting and providing guidance on how the HIPAA Privacy Rule applies to use and disclosure of health information.

Other federal departments and agencies, such as the National Institutes of Health (NIH), the Department of Veterans Affairs, and the Department of Defense conduct or support research involving the collection, storage and distribution of human specimens and associated data for research. In addition to complying with the Common Rule and FDA regulations, as appropriate, these departments and agencies have additional policies that apply to research that they support or conduct.

IRBs comprise another set of stakeholders, as they play a key role in overseeing the ethical collection, storage, and distribution of human specimens for research. They are responsible for ensuring that subjects' rights and welfare are protected in specimen banking and research projects involving human specimens and that those projects meet the requirements of their institutions as well as federal, state, and local regulations. IRBs and Privacy Boards also have roles in granting waivers of authorization as provided under the Privacy Rule.

Institutions and their legal officers are crucial stakeholders with responsibility for protecting subjects and providing the necessary infrastructure and research tools (such as specimen banks) to facilitate research.

Finally, and most important, individual subjects and society at large have an enormous interest in ensuring that research using specimens is ethically conducted. Individuals and society can help overcome the legal and ethical challenges to the effective collection, storage, and distribution of specimens for research, which will advance scientific knowledge and promote the public's health. Those who consent to the research use of their specimens must be assured that their rights and welfare will be protected. Maintaining the public trust is critical to ensure the continued participation of subjects in research and therefore vital to the entire research enterprise.

Types of Specimen Banks

In this paper, we use the terms "bank" and "repository" generically to describe a wide variety of collections of human specimens. In simple terms, a bank is a place that receives, stores, and disburses material. Storage may be long-term or short-term. Some repositories collect specimens prospectively to meet specific investigator requests (prospective collection) and store those

specimens only until they are shipped to recipient investigators. Banks can passively hold or store specimens or they can process human specimens to create derivatives.

As noted previously, a major challenge to developing a consistent set of policies and procedures for collecting, storing, banking, and distributing specimens for research is the wide range and variability of banks. (Table 1 illustrates some relevant characteristics of banks.)

In general, specimens and/or data collections can be organized in a variety of ways. These include individual, private collections residing in a single investigator’s laboratory or large well-annotated banks or collections of specimens and/or data that are used by multiple researchers, each with separate research projects. Some repositories or databases collect specimens and/or data specifically for distribution to researchers. Specimen banks may have a single collection and/or storage site or have multiple collection and/or storage sites.

Banks may also contain varying amounts of patient identifying information. Some specimen or data collections have data that is completely anonymous and have not way to link the identity of their subjects to their data. Others may provide a link to the subject’s identity, but provide specimens and data to researcher only in coded form without any identifying information. Specimens and/or data may also be identifiable, that is they are associated with direct personal identifiers (e.g. names or patient numbers) in order to allow additional information to be obtained on the subjects in the future.

The nature and extent of associated data and how these data are protected is critical to the level of risk involved in specimen research. The details of how a bank obtains its materials; how the materials are stored and how they are dispersed have implications for compliance with federal regulations, IRB review, risk assessment, and consent and authorization requirements.

Thus, the fact that there are so many models of banks makes it difficult to develop a “one-size-fits-all” approach to management and oversight.

Table 1: Variable Dimensions of Banks

Dimension	Variation
Primary purpose of specimen collection	-clinical care -clinical care with subsequent research use -research <ul style="list-style-type: none"> • placement in a bank was the primary research goal • placement in a bank was anticipated at the time of subject enrollment • placement in a bank was not anticipated at the time of subject enrollment
Populations represented in the bank	-general population -patients with specific diseases -specialized or vulnerable populations -clinical trial or other research subjects
Who can provide human	-any investigator or clinician

specimens to the bank?	<ul style="list-style-type: none"> -approved investigators or clinicians -only investigators or clinicians within the ‘home’ institution -only investigators or clinicians outside the ‘home’ institution <ul style="list-style-type: none"> •authorized depositors •any depositor
Who can access specimens from the bank?	<ul style="list-style-type: none"> -investigators from the repository’s institution: <ul style="list-style-type: none"> • any investigator • approved investigators -investigators external to the repository’s institution <ul style="list-style-type: none"> • any investigator • investigators from not-for profit institutions • investigators from commercial institutions • investigators meeting specific criteria
Scope of banked material	<ul style="list-style-type: none"> -type of human specimens: <ul style="list-style-type: none"> • single disease/condition/type of specimen • multiple specified diseases/conditions/ types of specimens • global – no limitations -types of associated data <ul style="list-style-type: none"> • demographics and pathology diagnosis • clinical information • research data
Custodianship	<ul style="list-style-type: none"> -academic medical center <ul style="list-style-type: none"> • individual investigator • individual department/division • institutional -academic consortium -federal agency (e.g., NIH) -industry -private <ul style="list-style-type: none"> • specific advocacy group • not-for profit multi-use bank
HIPAA Privacy Rule status of bank	<ul style="list-style-type: none"> -covered entity -not a covered entity
Physical location	<ul style="list-style-type: none"> -single site -multiple sites <ul style="list-style-type: none"> • loosely affiliated cooperating banks • network with centralized coordinating center • virtual bank

Identifiability of banked materials	-identifiable (according to Common Rule or HIPAA Privacy Rule) -coded -HIPAA Privacy Rule Limited Data Set -anonymous and/or HIPAA de-identified
Identifiability of distributed materials	-identifiable (according to Common Rule or HIPAA Privacy Rule) -coded -HIPAA Privacy Rule Limited Data Set -anonymous and/or HIPAA Privacy Rule de-identified
Identifier processing by the bank	-identifiers are left in place -limited data set -coded (linked to subject identity) -anonymous (no link to subject identity) <ul style="list-style-type: none"> • converts limited data set to anonymous • converts coded to anonymous
Specimen processing	-none -frozen -mince and place in media -formalin fix-paraffin embed -make derivative product/s (e.g., protein, DNA)

**BARRIERS TO THE COLLECTION, STORAGE, DISTRIBUTION,
AND RESEARCH USE OF HUMAN SPECIMENS**

The working group identified the following major barriers that deserve attention and must be overcome to facilitate the ethical and appropriate use of human specimens in research:

1. Diversity of banks and confusion about what types of banking activities constitute research activities or human subjects research under existing regulations.
2. Lack of a single comprehensive ethical and regulatory framework that addresses the full spectrum of activities related to specimen banking and use. The current situation is a patchwork of regulations and guidance addressing the collection, storage, distribution, and use of human specimens and associated data.
3. Lack of harmony among federal regulations.
4. Misunderstanding and over interpretation of the risks associated with the banking and use of specimens
5. Differing and confusing regulatory requirements for obtaining informed consent for the use of specimens in research and the HIPAA Privacy Rule requirement for authorization for the research use of protected health information.
6. Practical implementation issues related to informed consent and authorization.
7. The HIPAA Privacy Rule imposition of additional requirements for research that is covered by the Common Rule, adding unnecessary burden to patients, researchers, IRBs, and institutions.

Each barrier is discussed below and recommendations that may overcome these barriers are made.

The following barriers were identified but not addressed by this group. Further discussion and recommendations by a future group are merited. Given their importance, these barriers at the least deserve mention.

- Lack of clear guidance about how to deal with the complex issues of ownership of specimens, intellectual property considerations with regard to discoveries made using specimens.
- Whether research results should be returned to subjects and if so, how and when.

BARRIER 1: Diversity of banks and confusion about what types of banks constitute research activities under existing regulations

As illustrated in Table 1, specimen banks share some similarities but can also have significant differences. They might involve different sets of interested parties, for example, the collectors of the samples, those responsible for storage and data management, recipient investigators and the sponsors of the research. The specimen collector or bank personnel may also conduct research, or may only collect and store materials for others to use. Given these differences, should all collections be subject to the same regulations and policies?

A primary confusion lies in determining when a bank or specific banking activities are in fact research for the purposes of regulatory oversight. The Common Rule defines research as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.” Some have argued that the creation of a repository to support future research is not research. They point out that such a repository is a research tool with no hypothesis-driven or research-driven mission and that repository staff is not engaged in research on the specimens. In contrast, OHRP considers creation or operation of a human specimen or a data repository to support future research to be a research activity and subject to regulation. However, no guidance exists about whether these interpretations apply to the entire spectrum of banks. For example, many would agree that a bank is involved in research if it was constituted solely for actively collecting and maintaining specimens for research. Many would agree that the bank is NOT involved in research if it was constituted primarily for clinical purposes (e.g., pathology department archives) and may (or may not) be used as a source of research specimens. But what about the situation where a general, broad-scope bank is created for the purposes of clinical care but used for both research and internal operations (e.g., quality assurance)? Does the mere use of existing clinical specimens for research (the policy of many pathology departments) mean a bank is engaged in research? Does a bank’s status change if it was established for both clinical and research uses?

Current interpretation of the Privacy Rule is that the creation of a specimen bank or data repository and the use or disclosure of protected health information obtained from such a repository for research purposes constitutes a research activity under the regulations. However, the Privacy Rule would only apply if the organization maintaining the specimen repository is a “covered entity” as defined under the HIPAA Privacy Rule. It is important to further clarify that a repository maintained and used for clinical care and/or operations has fewer requirements under the Privacy Rule than does a research repository. There are difficulties and confusion when a bank is involved in several activities (i.e., patient care and research) and the use of

human specimens stored in the bank can shift from one use to another, for example, from clinical care or quality assurance to research or vice versa.

As a first step, it would be helpful for institutions maintaining or creating human specimens collections to have better regulatory guidance on when specific activities are considered research and the circumstances under which they are covered by each set of federal regulations.

Recommendation to Federal Regulatory and Funding Agencies

A: OHRP should provide criteria for and examples of when a “collection” of human specimens is considered a research activity under the Common Rule. Specific attention should be paid to multiple-use and research support collections. OHRP should re-evaluate whether the mere collection of excess specimens for possible future use constitutes research for the purposes of regulatory oversight.

BARRIER 2: Lack of a comprehensive ethical and regulatory framework that addresses the full spectrum of activities related to specimen banking and use.

In the United States, the Common Rule has been the regulatory policy followed by 17 federal departments and agencies for protecting human research subjects. Each codification of the Common Rule by a department or agency is equivalent to 45 CFR 46, Subpart A, the DHHS codification. The Common Rule applies to all research involving human subjects “conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make this policy applicable to such research.”

FDA, while a signatory to the Common Rule, has separate regulatory authority over research involving food and color additives, investigational drugs, medical devices, biological products intended for human use and being developed for marketing, and electronic products that emit radiation. For example, FDA regulations apply to the use of specimens for the development of an assay for which marketing approval would be sought. To this research, FDA also applies its own regulations, which are generally but not entirely the same as the Common Rule.

Even though these federal regulations cover a large portion of human research conducted domestically, and in some cases internationally, they are limited in their reach. In fact, if federal funds are not involved or if FDA premarket approval is not required, research activities involving human subjects are not subject to any form of federal regulatory oversight. However, many institutions with an OHRP-approved Federal-wide Assurance have agreed to apply the Common Rule to all human subject research conducted at or supported by their institutions, regardless of the source of funding.

The Privacy Rule applies to some research activities at an institution if the institution falls within the HIPAA Privacy Rule definition of a “covered entity” (health plans, health care clearinghouses, or health care providers who transmit health information for certain transactions as defined by DHHS) or by business associates acting for a covered entity. The Privacy Rule does not apply to specimens per se, but it may apply to the identifiable health information associated with specimens. Confusion relating to human specimen banking results because there is no universal correct application of HIPAA Privacy Rule: some research institutions are not

covered by HIPAA and hybrid HIPAA entities may or may not consider research a HIPAA Privacy Rule-covered activity. Detailed guidance has been developed by the NIH and the HHS Office of Civil Rights (OCR)⁴.

Existing guidance related to research use of human specimens and data consists of a patchwork of documents issued by OHRP, NIH, FDA and OCR, none of which comprehensively cover the full spectrum of activities and issues related to human specimen collection, storage, distribution and use. Relevant documents that address banking activities and the use of specimens and associated data include the following:

- OHRP: Issues to Consider in the Research Use of Stored Data or Tissues, guidance memorandum issued in November 1997⁵
- OHRP: Engagement of Institutions in Research, guidance memorandum issued January 26, 1999⁶
- OHRP: Guidance on Research Involving Coded Private Information or Biological Specimens, issued August 10, 2004⁷
- NIH: Research Repositories, Databases and the HIPAA Privacy Rule issued July 2, 2004⁸
- NIH: Institutional Review Boards and the HIPAA Privacy Rule, issued July 8, 2004⁹
- FDA¹⁰ Guidance on Informed Consent for *In Vitro* Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable. issued April 25, 2006

Recommendation to Federal Regulatory and Funding Agencies

B: OHRP, FDA, NIH, and other relevant federal funding agencies should work with other stakeholders (e.g., researchers, repository managers, IRBs, lawyers, ethicists, patient advocates, and research subjects) to develop a comprehensive framework for the collection, banking, and use of human specimens in research.

BARRIER 3: Lack of Harmony among Federal Regulations in Terms of Scope, Terminology, and Applicability

The lack of a comprehensive approach that applies to the full spectrum of activities related to banking, including the collection, storage, distribution, and use of human specimens and associated data produces gaps in the guidance, overlap in some areas, and a lack of clarity that creates considerable confusion.

The Common Rule, FDA regulations, and the HIPAA Privacy Rule differ in several important respects that make it difficult for IRBs to review repository protocols and for researchers and repository managers to determine how to apply the regulations to their studies. These differences include:

- Inconsistent and different regulatory scope

⁴ <http://www.hhs.gov/ocr/hipaa/>

⁵ <http://www.hhs.gov/ohrp/humansubjects/guidance/reposit.htm>

⁶ <http://www.hhs.gov/ohrp/humansubjects/assurance/engage.htm>

⁷ <http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf>

⁸ http://privacyruleandresearch.nih.gov/research_repositories.asp

⁹ <http://privacyruleandresearch.nih.gov/irbandprivacyrule.asp>

¹⁰ <http://crpac.od.nih.gov/FinalFDAGuidanceonICforIVDDDeviceStudieswithLeftoverSpecimensthatAreNotIndividuallyIdentifiable.pdf>

- Inconsistent terminology, and
- Differences in the ability to grant exemptions and exceptions.

Inconsistent and Differing Regulatory Scope

As discussed earlier, there are three major regulatory regimes relevant to the banking and use of human specimens in research: the Common Rule, FDA regulations, and the HIPAA Privacy Rule. Activities of banks and investigators could be subject to some, all or none of the regulations. Determining which regulations apply can be confusing, particularly because of the inconsistent terminology used in the regulations.

In particular, the applicability of specific regulations is determined by several interrelated questions. The answer to each of these questions is in turn determined by the definition of key words. For the Common Rule, the basic questions are:

- Is the activity research?
 - If so, does the research involve human subjects?
 - If so, is the research exempt from the regulations?

The answers to these questions are determined according to the regulatory definitions of “research,” “human subject,” and “identifiability.”

What is Research?

As discussed earlier, the Common Rule defines research as a “systematic investigation ...designed to develop or contribute to generalizable knowledge...” However, FDA has no equivalent definition. Under the FDA regulations, the objective to generate data/information for submission to FDA or to be available for FDA inspection is the key to whether the research activity is under FDA jurisdiction. The agency uses the term “clinical investigation,” rather than the term “research.”

The Privacy Rule definition for the term research is similar to that of the Common Rule in that both focus on the intent to develop or contribute to generalizable knowledge as the key to determining whether or not an activity is research.

What is a Human Subject?

Both FDA regulations and the Common Rule use the term “human subject” as the focus of the system of protections, but they do not define the term in the same way. This creates confusion for all types of human subject research, but particularly for human specimen research.

The Common Rule provides the following definitions:

Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.

Intervention includes both physical procedures, by which data are gathered (for example,

venipuncture), and manipulations of the subject or the subject's environment that are performed for research purposes.

Interaction includes communication or interpersonal contact between investigator and subject.

Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

OHRP has tried to clarify what constitutes human subjects research in the context of research with human specimens. OHRP's *Guidance on Research Involving Coded Private Information or Biological Specimens*¹¹ states that research involving only coded¹² private information or specimens does not involve human subjects if the following conditions are both met:

1. the private information of specimens was 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 identity of the individual(s) to whom the coded private information or specimens pertain because, for example:
 - a. a key to decipher the code is destroyed before the research begins;
 - b. the investigators and the holder of the individual identifiers enter into an agreement prohibiting the release of individual identifiers to the investigators under any circumstances, until the individuals are deceased;
 - c. there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of individual identifiers to the investigators under any circumstances, until the individuals are deceased; or
 - d. there are other legal requirements prohibiting the release of individual identifiers to the investigators, until the individuals are deceased.

Investigator is anyone involved in conducting the research. The act of providing coded private information or specimens (e.g., from a specimen repository) does not constitute involvement in the conduct of the research. However, individuals are involved in the conduct of the research if they provide coded information or specimens and also participate on any other activities related to the research. Examples of participation include, but are not limited to, (1) the study, interpretation, or analysis of the data resulting from the coded information or specimens; and (2) authorship of presentations or manuscripts related to the research.

¹¹ <http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf>

¹² (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.

In contrast to OHRP's expansive guidance, FDA offers little guidance on interpretation of its regulations. FDA regulations at 21 CFR 50.3(g) and 56.102(e) provide the following definitions:

Human subject means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient.

FDA regulations at 21 CFR 812.3(p) further elaborates, stating:

Subject means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control.

Thus, according to FDA regulations any specimen used in device research involves a human subject even if the identity of the source of the material is not identifiable. This issue was addressed in the recent *FDA Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable*.¹¹

Another area of confusion arises in determining whether deceased persons are human subjects under these and other regulations. Specimens or associated data that are obtained from deceased individuals (e.g., autopsy materials) are not covered by the Common Rule or FDA regulations, but other federal regulations and state and local laws may apply.

The Privacy Rule covers deceased persons, but only requires that certain representations be obtained from the researcher seeking access to protected health information (e.g. that the use and disclosure is solely for research, is necessary for the research, and documentation, if requested by the covered entity, of the death of the individuals whose information is sought by the researchers). The covered entity must be able to provide information on such disclosures if requested by the decedent's personal representative.

What is Identifiable?

A key concept involved in determining the applicability of the Common Rule and the HIPAA Privacy Rule and the level of oversight required for banking activities is the degree of identifiability of specimens and/or data. The extent to which biological material can be linked to the person from whom it was obtained affects the risk involved to subjects and the necessary procedures that should be implemented to protect those subjects.

It is well recognized that specimens are more valuable if relevant clinical information about the person who provides the specimen is known. As a result, in an effort to maximize the value of specimens, banks often keep a record of that individual's identity. There are many ways of doing this, for example, a database of identifiable information could be physically maintained at the bank or a log of provider information could be kept separate from the main database in a coded or encrypted manner. If the bank can identify individuals, they are then able to obtain relevant additional or future clinical information (e.g., clinical outcome such as death due to disease or the occurrence of other disease processes related or non-related to the original specimen). Future information can be obtained in a variety of ways, each of which raises different confidentiality concerns and regulatory requirements. Data can be updated routinely at set intervals at the request of an investigator or a researcher could review the medical record directly.

FDA regulations, unlike the Common Rule, do not state that individually identifiable information is required to define a human subject or whether the identity of the subject must be “readily ascertainable” to the investigator. In fact, the FDA definition of human subject only defines a subject as anyone who is or becomes a participant in research. The recent *FDA Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable* clearly states that unidentified specimens require consent, but indicates that the agency will allow certain types of studies to be conducted without consent via the mechanism of enforcement discretion.¹³

To further complicate matters, the HIPAA Privacy Rule provides yet another definition of individually identifiable information, which is far more prescriptive than the Common Rule definition of individually identifiable. It provides the following definition:

Individually Identifiable Health Information: A subset of health information, created or received by a covered entity or employer and related to past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present or future payment for provision of health, and that identifies the individual or there is a reasonable basis to believe the information can be used to identify the individual (45 CFR part 160, and Subparts A & E of part 164).

The Privacy Rule covers identifiable health information stored in a covered entity. According to the Privacy Rule, information is de-identified if 18 specific identifiers have been removed, and the information cannot otherwise be used to identify the patient to whom the information pertains. Alternatively, "a person with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable" may certify that there is a "very small" risk that the information could be used by the recipient to identify the individual.

One common question is whether data are considered de-identified if they are identified with a code that allows re-identification of the subject. The Privacy Rule explicitly states that health information is de-identified even if it has been assigned and retains a code or other means of record identification, provided that the code is not derived from or related to any of the 18 identifiers and could not be used to identify the individual and that the covered entity does not use or disclose the code for other purposes or disclose the mechanism for re-identification.

Thus, determination of identifiability differs between the Common Rule and the Privacy Rule. Some coded information would be considered individually identifiable according to the HIPAA Privacy Rule, but not identifiable according to the Common Rule and vice versa. This makes it difficult for investigators, specimen repositories, and IRBs to be sure that the regulations are being followed.

Recommendations to Regulatory and Funding Agencies

C: Federal regulatory and funding agencies should develop standardized language and definitions for use in regulations, policy documents, and educational materials related to specimen banking.

¹³ <http://0-www.fda.gov.lilac.une.edu/cdrh/oivd/guidance/1588.html>

D: FDA should explore whether there are ways to more closely align the FDA definition of human subject with the Common Rule definition, which requires obtaining data through a research intervention or interaction or the use of individually identifiable information.

Common Rule Exemptions

Not all research using identifiable human specimens obtained from living individuals requires IRB review and approval. The Common Rule has a number of exemptions covering certain research situations (45 CFR 46.101(b) and other agency cites). An institution can determine that research that meets the criteria for such exemptions does not require IRB review and approval or informed consent. The exemption that applies most often to the collection, use, and distribution of human biological specimens and associated data is Exemption #4: (45 CFR 46.101(b)(4)):

Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

There are two components to this exemption that require comment. First is the phrase “publicly available.” This was originally intended to apply to data that were in the public domain and hence available to anyone (e.g., birth records, census data). Applying this to collections of human specimens is more complex. Many organizations (e.g., academic health centers) make human cells and specimens broadly accessible to the research community. Commercial companies allow investigators to purchase human specimens from their banks. Do these activities meet the standard of being publicly available?

The second component is the requirement for “existing” specimens. This means that the specimens should exist (“be on the shelf” or in the freezer) at the time the research is submitted to the entity (e.g. IRB or individual designated to make exemption determinations for the institution). For example, the human specimens must exist before the protocol is submitted to the institutional official or IRB to determine whether or not the research is indeed exempt. This precludes the prospective identification and/or collection of such specimens.

The Privacy Rule does not recognize these exemptions. Some research involving human specimens that is exempt under the Common Rule may be subject to the Privacy Rule. For example, chart reviews where data is recorded in such a way that the subjects cannot be identified either directly or indirectly through coding systems is exempt under the Common Rule, and neither IRB approval nor informed consent is required. However, an authorization, waiver of authorization, or use of a limited data set with data use agreement would be required in this example if information that is considered protected under the Privacy Rule is used for research, unless the ‘preparatory to research’ provisions of the Privacy Rule have been met. The FDA regulations do not have any exemptions except for emergency use, again suggesting that all specimens used in research submitted to the FDA are subject to FDA regulations whether or not they are identifiable.

Recommendations to Regulatory and Funding Agencies

E: OHRP should define more specifically when research using human specimens and associated data is or is not human subjects research and when it is exempt under the Common Rule.

Case studies and examples would help clarify the confusion in this area.

F: DHHS should modify the Privacy Rule to exempt all research that is exempt under the Common Rule.

BARRIER 4: Misunderstanding and over interpretation of the risks associated with the banking and use of specimens for research.

A major barrier to research on human specimens is the difficulty in evaluating risk. Assessing the level of risk and potential benefits of research is arguably the most important and challenging responsibility of an IRB. While risk assessment is critical in determining the regulatory requirements, the risks of collection, storage, distribution, and use of specimens are not generally well delineated or understood. There can be physical risks to subjects if specimens are collected specifically for research purposes through an intervention (e.g. a blood draw, or taking additional biopsies), but the primary risks for much specimen research relate to the loss of privacy and confidentiality. Such risks can be readily mitigated by well established operating procedures and policies of banks that protect patient privacy and confidentiality.

Federal regulations provide a framework by classifying research as involving either minimal risk or greater than minimal risk:

Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45 CFR 46.102(i); 21 CFR 56.102(i) and other agency cites).

Research involving more than minimal risk requires review by a convened IRB. In addition, research that poses greater than minimal risk must be conducted with full informed consent (consent cannot be waived or altered) except under limited circumstances that are not usually applicable to research involving human specimens.

The Privacy Rule has a more limited focus on risks of disclosures of protected health information and is relevant to research with human specimens when associated health information is obtained or maintained by a covered entity.

One considerable area of confusion in assessing risk is the common assumption that specimen research is often genetic research and risks associated with genetic information are always more than minimal. In fact, genetic research presents a spectrum of risk similar to other kinds of research. Additionally, the term “genetic research” is often used without appropriate specificity regarding the type of genetic information, the type of disease or condition being studied, etc. Studies of germline genetic research (familial or hereditary genetic research) have implications for family members and could in some cases involve greater risk to subjects or their families. However, risks associated with family studies can vary greatly and will depend on mediating factors such as the penetrance of the gene and the seriousness of the resulting condition. In

contrast, research on somatic mutations does not necessarily have the same implications for family members. It is important to put genetics research into context when evaluating risks.

Common misconceptions about genetic risk were described in a report of the Consortium on Pharmacogenetics in 2002, which brought together bioethicists, scientists, industry and policy experts to discuss legal and ethical issues in research and clinical practice. The Consortium described three fallacies of genetic risk:¹⁴

- Genetic exceptionalism – the assumption that all things genetic involve especially serious or unique ethical risk and therefore require novel ethical principles and/or special regulatory responses
- Genetic determinism – the assumption that genes are autonomous, self-sufficient causes of disease, overlooking the importance of environment and over-estimating the risks posed by information about genes
- Genetic overgeneralization – the failure to appreciate the heterogeneity of “genetic tests” and their results, so far as psychosocial risk is concerned (e.g., tests for a fatal single gene dominant disorder vs. tests for drug efficacy).

These misunderstandings have been confounded by concerns that coded or anonymized sequenced DNA from human specimens could be linked to individuals. To date, this issue has not been well explored and no guidance has been proposed.

Anecdotal evidence suggests that misunderstanding about risks and over estimation of risks associated with genetic studies creates a disconnect between the actual level of risk involved in collecting, storing, and using human specimens and the implementation of the regulatory requirements by IRBs. In its report *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance* (1999),¹⁵ the National Bioethics Advisory Commission noted that a great deal of the human specimen research that currently is conducted should be considered minimal risk research. NBAC also noted that specimen research may be considered minimal risk if confidentiality and privacy are protected and if the research plan includes consideration of whether and how to reveal findings to the subject. The authors agree with this assessment and believe that the regulatory agencies should clarify for IRBs and Privacy Boards how to assess risks for banking activities and what they can do to minimize risks associated with such activities.

Recommendation to Federal Regulatory and Funding Agencies

G: OHRP should develop additional guidance to help IRBs assess the level of risk related to the collection, storage, distribution, and research use of specimens and associated data.

H: DHHS/OCR should work with OHRP to develop additional guidance to help IRBs and Privacy Boards evaluate risks to privacy and confidentiality with a view toward improving consistency of subject privacy protections.

¹⁴ A Buchanan, A Califano, J Kahn, E McPherson, J. Pharmacogenetics: Ethical Issues and Policy Options. Kennedy Institute of Ethics Journal - Volume 12, Number 1, March 2002, pp. 1-15. The Johns Hopkins University Press. www.genomeutwin.org/events/Prevalent%20misapprehensions%20in%20debates.ppt

¹⁵ <http://www.georgetown.edu/research/nrcbl/nbac/pubs.html>

I: Federal regulatory and funding agencies should work with appropriate stakeholders to develop additional educational materials for IRBs, patients and the public about how to evaluate the benefits and risks of participation in genetics research on human specimens.

BARRIER 5: Differing and confusing regulatory requirements for obtaining informed consent for the use of specimens in research.

There are substantial and often confusing differences between the Common Rule and FDA requirements for informed consent and the HIPAA Privacy Rule requirements related to authorization. While consent and authorization are addressed in more detail later in this section, the primary confusion lies in the following areas:

- The difference between informed consent and authorization.
 - Informed consent is the process by which subjects are informed about the risks and benefits of taking part in a research project.
 - Authorization is solely a permission to allow researchers to use or disclose defined protected health information.

The scope of what is allowed or required for informed consent and authorization.

- OHRP and FDA allow consideration of informed consent for future unspecified research using human specimens, whereas the Privacy Rule requires the authorization to be study-specific.¹⁶
- The Common Rule allows a waiver of the informed consent under certain conditions. The Privacy Rule allows waiver of authorization under similar but not identical conditions.
- FDA regulations limit waiver to emergency research.

When discussing informed consent and authorization, it is important to acknowledge that there are two separate points at which consent/authorization must be considered. The first is when human specimens and associated data are entered into a bank, and the second is when researchers access human specimens and associated data from the bank.

Common Rule Requirements

While the default position in the Common Rule is that informed consent is required, IRBs are allowed under the regulations to waive or alter informed consent when the following conditions are met.

- the research involves no more than minimal risk to the subjects,
- the waiver or alteration of consent will not adversely affect the rights and welfare of the subjects,
- the research could not practicably be carried out without the waiver or alteration, and
- whenever appropriate, the subjects will be provided with additional pertinent information after participation (45 CFR 46.116(d)).

¹⁶ IRBs and the Privacy Rule (<http://privacyruleandresearch.nih.gov/irbandprivacyrule.asp>)

Deciding when it is appropriate to waive consent for research involving the collection, storage, distribution, and use of specimens for research is difficult for a number of reasons. As discussed above, it is often unclear when research using human specimens and data constitutes more than minimal risk. In addition, as noted by NBAC in its report on human biological materials, “practicability” in terms of waiving consent has not been defined. It can be difficult for an IRB to determine when it is impracticable to obtain consent. Neither OHRP nor OCR has any current guidance on the meaning of practicability as a criterion for waiver of consent or authorization.

The Canadian Institutes of Health Research has published criteria for determining when obtaining informed consent for use of existing datasets is impracticable¹⁷.

These include:

1. The size of the population being researched;
2. The proportion of individuals likely to have relocated or died since the time the personal information was originally collected;
3. The risk of introducing potential bias into the research thereby affecting the generalizability and validity of results;
4. The risk of creating additional threats to privacy by having to link otherwise de-identified data with nominal identifiers in order to contact individuals to seek their consent;
5. The risk of inflicting psychological, social or other harm by contacting individuals or families with particular conditions or in certain circumstances;
6. The difficulty of contacting individuals directly when there is no existing or continuing relationship between the organization and the individuals;
7. The difficulty of contacting individuals indirectly through public means, such as advertisements and notices; and
8. Whether, in any of the above circumstances, the requirement for additional financial, material, human, organizational and other resources needed to obtain such consent will impose an undue hardship on the organization.

These criteria appear to be complete, reasonable and appropriate. OHRP and the other regulatory agencies should consider their usefulness for determining practicability.

Recommendation to Federal Regulatory and Funding Agencies

J: OHRP should issue guidance clarifying when waiver of informed consent for collection, storage, distribution, and use of specimens in research is appropriate. This should include:

- i) guidance on determining when research using biological specimens is minimal risk*
- ii) guidance on interpreting the “practicability” requirement for waiver of informed consent.*

Another area of concern relates to the information provided during the informed consent process. The informed consent process should describe the risks and benefits of the research and provide subjects enough information to allow them to make an informed choice about whether or not to participate. Ideally, the consent obtained at the time of acquiring specimens for placement into a bank should include a description of the type of research that the specimens will support. However, in many cases, it is not possible to describe future uses with any degree of specificity.

¹⁷ CIHR Best Practices for Protecting Privacy in Health Research, p15. September 2005.
http://www.ocr.ca/ehp/presentations/Best_Practices.pdf

This has resulted in some disagreement about the adequacy of the consent process. Some believe that consent is not in fact informed unless all specific research uses can be described, while others believe a general consent for future uses of specimens is sufficient. Recent studies suggest that, when asked, most research participants will prospectively authorize consent for future use of specimens.^{18,19,20}

OHRP's interpretation of the Common Rule allows generalized informed consent for future research use of specimens and associated data (see NIH: Institutional Review Boards and the HIPAA Privacy Rule, issued July 8, 2004; <http://privacyruleandresearch.nih.gov/irbandprivacyrule.asp>). Existing model consent forms such as the National Cancer Institute-National Action Plan for Breast Cancer Model Consent (<http://www.cancerdiagnosis.nci.nih.gov/specimens/legal.html>), were designed to obtain informed consent for future unspecified research and have been used extensively. Additional guidance on the use of such consent forms and endorsement of specific approaches by OHRP would reduce concerns of investigators and IRBs and help minimize variability in IRB behavior.

Recommendation to Federal Regulatory and Funding Agencies

K: OHRP should provide additional guidance about the use of generalized informed consent for future research use of specimens and associated data and develop acceptable consent models for specimen banking.

FDA Requirements

FDA regulations have no provision for waiver of consent. Section 520(g) of the Federal Food, Drug, and Cosmetic Act, which provides regulations for investigations of medical devices (which may include diagnostic tests), requires that IRB review (520(g)(3)(A)) and informed consent (520(g)(3)(D)) be obtained for all clinical investigations of medical devices, except in certain emergency circumstances.

Because it may not be possible or practical to obtain informed consent for research use of specimens and data under some defined circumstances, approaches should be explored to allow minimal risk research involving specimens to be conducted without informed consent. The new FDA guidance discussed earlier is a good beginning, but could be extended to cover more cases. For example, research use of excess specimens collected for routine clinical care should be permitted without consent if risks to the subjects are minimal.

The recent FDA *Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable* states that

¹⁸ Chen, D. T., Rosenstein, D. L., Mathappan, P., Hilsenbeck, S. G., Miller, F. G., Emanuel, E. J., Wendler, D., "Research With Stored Biological Samples: What Do Research Participants Want?" *Arch. Intern Med.* 2005, 165: 652 – 655.

¹⁹ Malone, T., Catalano, P. J., O'Dwyer, P. J., Giantonio, B., "High Rate of Consent to Bank Biologic Samples for Future Research: the Eastern Cooperative Oncology Group Experience." *J. Natl Cancer Inst.* 2002; 94: 769-771.

²⁰ McQuillan, G. M., Porter, K. S., Agelli, M., Kington, R., "Consent for Genetic Research in a General Population: the NHANES Experience." *Genet. Med.* 2003; 5: 35-42.

FDA does not intend to object to the use, without informed consent, of leftover human specimens -- remnants of specimens collected for routine clinical care or analysis that would otherwise have been discarded -- in investigations that meet the criteria for exemption from the Investigational Device Exemptions (IDE) regulation at 21 CFR 812.2(c)(3), as long as subject privacy is protected by using only specimens that are not individually identifiable. FDA also intends to include in this policy specimens obtained from specimen repositories and specimens that are leftover from specimens previously collected for other unrelated research, as long as these specimens are not individually identifiable.

This policy goes a long way toward addressing one of the major inconsistencies between the FDA human subjects regulations and the OHRP policy on the use of residual specimens.

Recommendation to Federal Regulatory and Funding Agencies

L: FDA should explore additional approaches to permit specimens and data to be used without consent for minimal risk research.

The requirements for the Privacy Rule waiver or alteration of the authorization requirement parallel those of the Common Rule but focus instead on minimal risk to privacy as opposed to minimal risk from all harms, as is described in the Common Rule.

According to the Privacy Rule, authorization is a permission for use and disclosure of protected health information, whereas consent under either the Common Rule or the FDA regulations is a process that provides information to and agreement from the subject to participate in the research as a whole. Although the Privacy Rule does not specifically include human specimens, it does have implications for associated protected health information that might be transmitted with a specimen.

Although authorization is generally required under the HIPAA Privacy Rule, authorization for the use or disclosure of protected health information is not required if one of the following applies:

Documentation that an IRB or Privacy Board has waived the authorization requirement in accordance with the conditions specified in section 164.512(i).

The use or disclosure of protected health information is for reviews preparatory to research with representations that satisfy section 164.512(i)(1)(ii) of the Privacy Rule. The use or disclosure of protected health information for research on decedents' with representations that satisfy section 164.512(i)(1)(iii) of the Privacy Rule.

Only a limited data set is provided and there is a data use agreement with the recipient as specified under section 164.514(e).

The use or disclosure of protected health information is based on permission obtained prior to the compliance date of the Privacy Rule as specified under section 164.532(c) of the Privacy Rule.

The covered entity has de-identified the protected health information according to standards set forth in the Privacy Rule so that its use and disclosure are not covered by the Privacy Rule.

A covered entity may also use or disclose protected health information from databases and banks for other purposes without authorization as permitted by the Privacy Rule, such as if required by law or to a public health authority for a public health activity (e.g., disclosures to cancer registries).

Current interpretation of the HIPAA Privacy Rule requires that an authorization must be study-specific and does not permit authorization for future unspecified use of protected health information. This is at odds with the OHRP and FDA interpretations of the human subjects regulations as described above. This is particularly relevant for human specimens banking. For example, when obtaining specimens from living individuals to create a repository established and maintained for research purposes, the IRB-approved informed consent document may include a description of the types of research that may be conducted as an indication of the fact that in the future there may be additional uses that cannot be anticipated. This would then allow the specimen bank to provide human specimens for research studies that could not have been anticipated when the specimens were collected.

Recommendation to Federal Regulatory and Funding Agencies

M: DHHS/OCR should explore approaches for removing the requirement that the authorization for research use of protected health information obtained from a research repository or database be study-specific.

The logistics of authorization are further complicated by the fact that an authorization to create and maintain a research database or repository may not be combined with an authorization for research in a clinical trial in which a subject may receive medical care. This restriction results from the desire to not make enrollment in research a condition of treatment. While perhaps a worthy goal, this is in contrast to what is allowed by the Common Rule and FDA regulations. The result can be multiple consent/authorization forms that cover the same activities in different ways. It also can result in long and complex authorization forms, which almost guarantee confusion and put additional burden on the person who provides the specimen. This restriction should be removed to simplify the consent and authorization process and lessen the burdens on patients.

Recommendation to Federal Regulatory and Funding Agencies

N: The Privacy Rule should be revised to allow authorization for use of protected health information collected as part of a clinical trial to cover both research and banking activities.

Under the Privacy Rule, covered entities are required to provide an accounting of disclosures of protected health information upon request to patients when the disclosures were made pursuant to a waiver of authorization. Accounting for disclosures of protected health information from a research repository or database when there has been a waiver of authorization poses a considerable burden on researchers, repository managers, and their institutions. By definition,

waivers of authorization may be granted only if the research is minimal risk. While the tracking of disclosures in this situation does allow an individual to learn, upon request, how his/her PHI has been disclosed, it does not proactively increase privacy protections. In fact, tracking may lead to decreased privacy for individuals by virtue of the need to maintain identifiable information in records disclosures.

Recommendation to Federal Regulatory and Funding Agencies

O: The Privacy Rule requirement to account for disclosures of protected health information pursuant to a waiver of authorization should be eliminated.

Barrier 6: Practical Implementation Issues Related to Informed Consent and Authorization

The process of obtaining consent and authorization raises a number of logistical issues. Human specimens can be obtained in a number of ways, and the manner in which they are obtained dictates to some degree the process for consent.

Obtaining human specimens specifically for research obviously requires the investigator to obtain informed consent and may require authorization. This includes situations in which the human specimens are collected solely for research purposes as well as those situations in which “excess” specimens are obtained during routine clinical care. For example, an investigator may plan to obtain an extra biopsy at the time of a routine biopsy, or an extra 5 cc of blood at the time of a routine phlebotomy. Because this involves intervention, it clearly requires consent.

The more difficult situation is the collection, immediately after pathology review, of identifiable human specimens that were obtained for clinical care and are in excess after the diagnosis is completed. Under the Common Rule, research using human specimens is currently considered human subjects research if primary identifiers are associated with those specimens. In this situation informed consent or a waiver of consent must be obtained. Given the prospective nature of the collection and the potential for a face-to-face interaction with the individual, IRBs might not consider a waiver of consent to be appropriate under these circumstances because it is difficult to fulfill the “impracticability” requirement in the Common Rule’s informed consent waiver criteria. In this latter situation, the clinician seeing the individual may not be an investigator and may not be familiar with human specimens banking. In this case, the treating clinician may be unable or unwilling to obtain a truly informed consent.

Obtaining consent can pose a huge barrier to institutional banking initiatives. Perhaps the biggest challenge is the time and expertise needed to inform every patient of the banking initiative in a busy medical practice.

Who should administer the consent process for specimens collected during the course of routine care? The personnel who collect human specimens and associated medical information are likely to be the most knowledgeable about the purposes of human specimens banking, but

generally do not have direct access to patients. They may never see, talk to, or otherwise interact with patients unless instructed to do so. Medical care providers often do not have the time or

commitment to obtain informed consent for the research, unless they are part of a defined research project.

Some have suggested that admitting clerks obtain consent during the registration or admission process. This is problematic for a number of reasons. Can the admitting clerk be made knowledgeable enough about human specimens banking to obtain informed consent? Many medical centers have hundreds of admission points into their system making it more difficult to maintain a level of expertise at each point. Furthermore, admission processes are already complicated, stressful, and filled with forms to sign.

Administering consent at other times in the admissions and treatment processes has also been considered. For example, some patients are admitted on the early morning of surgery and consent could be sought as they await surgery. However, many of these patients are pre-medicated, have little privacy in crowded waiting areas, and are often extremely stressed. Another time to administer consent would be following surgery or after admission for other forms of therapy. Much of the stress is removed, and access and privacy are much easier. But, most post-operative patients are on continuous and/or self administered morphine/morphine derivatives to control post-operative pain.

What about seeking consent from surgical patients at their clinic visits? Again, there are hundreds of clinics, limited personnel, no room for specimen resource personnel, and physicians who do not want their clinics disturbed. The problem is compounded for non-surgical patients. Obtaining informed consent/authorization can require up to an hour per patient, counting travel to and from the patient's room. Thus, there are considerable logistical challenges to obtaining informed consent and authorization for collection of excess specimens initially obtained for clinical care.

An additional challenge is the infrastructure needed for tracking who gave consent and authorization for what specific research activity/ies. This is particularly important when "tiered" consent is used and re-contact to obtain a new consent for specific future research is an option.

Some institutions are considering dedicated human specimens banking consent offices that would be staffed with trained research assistants knowledgeable in human specimens banking. A clinician would refer appropriate patients to the human specimens consenting office for a deliberate and truly informed process. Creating and maintaining this infrastructure requires space, personnel, and financial support.

Incorporating informed consent for future research on specimens into academic research hospital practice would allow greater control and oversight of the process than obtaining consent on a case-by-case basis. One approach would be to create and staff a specimen banking consent office to which every clinician could refer his/her patients as appropriate. Support for such an infrastructure would be required. One possibility would be for NIH to support such infrastructure through supplements to existing projects, for example, through General Clinical Research Center or Cancer Center grants.

Recommendation to the Federal Regulatory and Funding Agencies

P: Funding agencies should support infrastructure to enable institutions to implement processes for routinely obtaining and tracking informed consent for future research use of specimens obtained during the course of medical care.

Most research using human biological materials poses few risks. In addition, numerous studies indicate that subjects want their specimens to be used for research.^{9,10,11} Given the difficulties in obtaining explicit consent, alternatives to explicit consent should be considered. For example, currently, excess material from a specimen obtained for clinical diagnosis is kept in the pathology department for a specified period of time (by law). Once the diagnosis is finalized, the excess specimen is destroyed. Under a rigid reading of the current regulations, informed consent would be required from each person whose identifiable excess specimen is placed into a research repository rather than destroyed. An alternative approach that should be considered would be to simply notify patients that excess specimens will be banked for research. The notification could include an opt-out approach for those patients who did not want their specimens and associated data placed into a research bank.

This approach is similar to the Notice of Privacy Practice in the HIPAA Privacy Rule that can be used to inform patients of how their protected health information will be used by the covered entity. The Privacy Rule requires that individuals be given the right to opt out of some uses of their protected health information, but the institution has the right to not comply with this request. Excess specimens could seemingly be handled in a similar way.

The concept of notification is consistent with the public's willingness to have their biological materials used in research. Study after study has shown that people favor research use of their specimens and associated data. However, most want to be notified that such activities are likely to occur and that sufficient safeguards are in place to protect the disclosure of identified private information to third parties who have no interest in their rights and welfare (Jack and Womack, 2003; Malone et al., 2002; Schwartz et al., 2001; NBAC, 1999).²¹

Recommendation to Federal Regulatory and Funding Agencies

Q: OHRP should consider the acceptability of using alternative approaches to informed consent, such as 'opt out' notification, as a tool to be used in concert with a waiver of consent for future research on residual specimens.

Barrier 7: The HIPAA Privacy Rule imposes additional requirements on research that is covered by the Common Rule, which unnecessarily burdens patients, researchers, IRBs, and institutions

As mentioned previously, the lack of harmony among the Common Rule, FDA regulations, and the Privacy Rule creates confusion for patients and other subjects, researchers and repository managers, IRBs, and institutions. In addition, the Privacy Rule has certain provisions that are duplicative of the requirements of the Common Rule. For example, the Privacy Rule generally requires authorization for use and disclosure of protected health information for research, unless an exception applies. Many of the requirements for authorization are similar, but not identical to

²¹ <http://www.georgetown.edu/research/nrcbl/nbac/pubs.html>

the Common Rule. Patients may be asked to provide informed consent for research using their specimens and in addition asked to sign authorizations, if protected health information will be used and disclosed as part of the research. This results in complex, lengthy consent and authorization forms that are duplicative and sometimes conflicting.

The Common Rule requires that the risks and benefits of research be evaluated and that privacy risks be considered as a risk of the research. In addition, such risks should be discussed as part of the informed consent process. Thus, privacy risks should already be covered as part of the oversight process required by the Common Rule. It is not clear that a separate authorization for use and disclosure of protected health information for research purposes confers any additional protection to subjects. It may perhaps confuse them and divert their attention from other more significant risks of the research described in the consent form.

One approach for addressing the lack of harmony among the regulations and the confusion and burdens to patients and other subjects, researchers, IRBs and institutions imposed by the Privacy Rule would be to modify the Privacy Rule to exempt research that is covered by the Common Rule.

Recommendation to Federal Regulatory and Funding Agencies

R: DHHS should modify the Privacy Rule to exempt research that is subject to the Common Rule because the Common Rule provides appropriate and equivalent protections.

This approach offers the following advantages:

It would address the inconsistencies between the Common Rule and the Privacy Rule regarding the definition of "identifiable."

It would improve the consistency and review of information presented to the subject/patient regarding protection of privacy. (IRBs are not required to review free-standing HIPAA Privacy Rule authorizations – they only have to review the authorization that is included as part of the consent.)

It would eliminate the confusion and burden to subjects/patients of having to sign both an authorization and an informed consent form. Privacy and confidentiality protections could be addressed during the consent process and as part of the consent document.

It would allow institutions to consider waiver of informed consent alone and eliminate the need to also review waivers of authorization.

Privacy and confidentiality protections can be addressed in the informed consent process as one of the risks of the research.

SUMMARY AND CONCLUSIONS

As noted earlier, research using human specimens and data is proving increasingly important to the advancement of science yet substantial legal, ethical and policy challenges must be overcome if its promise is to be fulfilled. This White Paper summarizes and discusses these challenges in detail and, where appropriate, makes recommendations to federal regulatory and funding agencies. These recommendations constitute a consensus among the disparate stakeholders who composed the committee. We provide these recommendations in the spirit of cooperation and in the hope that the tangled web of diverse regulations and policies can be harmonized to remove unnecessary barriers to research involving human specimens and data, while at the same time protecting subjects. The hope is that by facilitating a common understanding of the applicable ethical and regulatory framework for research using human specimens and data, science can proceed more rapidly to reduce suffering and save human lives.

Part II of this report provides a number of tools that investigators, IRB members and repository managers can use to better understand the landscape of regulatory and ethical requirements for conducting the research.

**Report of the Public Responsibility in Medicine and
Research (PRIMR) Human Tissue/Specimen Banking
Working Group**

**Part II
Tools for Investigators, IRBs and Repository Managers**

March 2007

Contents:	Page
Tool A: Comparison of Common Rule, FDA Regulations and the HIPAA Privacy Rule ²²	1
Tool B: Common Rule Specific Issues	20
Tool C: How do FDA Regulations differ from the Common Rule?	25
Tool D: HIPAA Privacy Rule Issues for Repositories ²³	26
Tool E: Managing risks in the Context of Research using Human Specimens	37
Tool F: Patient attitudes:	42
Tool G: Reporting Research Results to Subjects:	47
Tool H: Ownership of specimens, commercialization and Intellectual property	50
Tool I: State Laws	53
Tool J: International Policies and Guidelines	57

²² Note that the HIPAA Security Rule, while not specifically discussed may also apply in some situations.

²³ International Society for Biological and Environmental Repositories Newsletter, Volume 4, Issue No. 1, Fall 2004 (<http://www.isber.org/newsletters/Fall2004.pdf>)

Tool A
**Comparison of Common Rule, FDA Regulations, HIPAA Privacy Rule and
 HIPAA Security Rule**

The following table provides a comparison of the three major regulations that apply to the use of human specimens and data for research with respect to their applicability and key definitions. In addition, the HIPAA Security Rule is described and compared where applicable with the HIPAA Privacy Rule.

Concept	objective
HHS OHRP Human Subjects Regulations 45 CFR 46	To protect the rights and welfare of human subjects involved in research conducted or supported by HHS
HHS FDA Human Subjects Regulations 21 CFR 50, 56 & 812	<ul style="list-style-type: none"> • “To protect the rights, safety and welfare of subjects involved in clinical investigations regulated by FDA...” (21 CFR part 50 & 56) • “To encourage... the discovery and development of useful devices intended for human use and ... to maintain optimum freedom for scientific investigators in the pursuit of this purpose.” (21 CFR 812)
HHS Privacy Rule 45 CFR 160 & 164 subparts A & e	<ul style="list-style-type: none"> • Establishes a Federal floor of privacy protections for most individually identifiable health information by establishing conditions for its use and disclosure by certain health care providers, health plans, and health care clearinghouses. This affects tissue banking in that individually identifiable health information often accompanies tissue specimens and is often needed for tracking purposes and longitudinal research.
Significant Differences:	<ul style="list-style-type: none"> • HHS and FDA regulations have the broader objective of protecting rights and welfare of human subjects, including but not limited to subjects’ privacy interests. • Privacy Rule (and Security Rule) focused more narrowly on protecting individuals’ privacy, confidentiality, and security interests in their health information. • Privacy Rule and Security Rule are not focused primarily on research. • Privacy Rule has detailed requirements for protecting the confidentiality of individually identifiable health information, including data associated with specimens.
Similarities:	<ul style="list-style-type: none"> • All address protecting privacy, confidentiality, security interests of human subjects

Concept	Applicability/Scope
HHS OHRP Human Subjects Regulations 45 CFR 46	<ul style="list-style-type: none"> • Applies only to non-exempt human subjects research conducted or supported by HHS. • Specifies six areas of research as exempt from the HHS regulations. The exemption that is typically most relevant to research involving repositories and human biological specimens (exemption 4) is: “research involving the collection or study of existing data, documents, records, pathological specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.” 45 CFR 46.101(b)(4).
HHS FDA Human Subjects Regulations 21 CFR 50, 56 & 812	<ul style="list-style-type: none"> • Applies to all clinical investigations regulated by the FDA under sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act (the Act), as well as clinical investigations that support applications for research or marketing permits for products regulated by the FDA, including foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products (“FDA regulated products”). • Additional specific obligations and commitments of, and standards of conduct for, persons who sponsor or monitor clinical investigations involving particular test articles may also be found in other parts (e.g., parts 312 and 812). Compliance with these parts is intended to protect the rights and safety of subjects involved in investigations filed with FDA. [See 21 CFR §50.1.] • 21 CFR part 56: Contains the general standards for the composition, operation, and responsibility of an IRB that reviews clinical investigations regulated by the FDA under sections 505(i) and 520(g) of the act, as well as clinical investigations that support applications for research or marketing permits for FDA regulated products. [See 21 CFR §56.101.] • When research subject to FDA jurisdiction is federally funded 45 CFR 46 would also apply. • 21 CFR 812.2(a): This part applies to all clinical investigations of devices to determine safety and effectiveness unless the device investigation is exempt under 812.2(c).
HHS Privacy Rule 45 CFR 160 & 164 subparts A & e	<ul style="list-style-type: none"> • Applies to covered entities; i.e., health care providers who transmit information in electronic form in connection with a HIPAA standard transaction, health plans and health care clearinghouses. • Within the context of tissue banking, the Privacy Rule applies to the transmission of information that is “appended” to the tissue in cases where the tissue and identifiable information appended to it is obtained or received by a HIPAA covered entity. • HIPAA does not treat tissue or blood as individually identifiable

	health information. See National Institutes of Health, Research Repositories, Databases, and the HIPAA Privacy Rule. ²⁴
Significant Differences:	<ul style="list-style-type: none"> • HHS regulations – Coverage hinges on funding source. • FDA regulations – Coverage hinges on whether activities are regulated by FDA. • Privacy Rule (and Security Rule) – Coverage hinges on whether individually identifiable information is held by covered entities or a covered entity’s business associate acting for the covered entity. • Unlike the HHS regulations, the Privacy Rule does not have “exempt research.” Therefore, some research involving repositories or human biological specimens may be exempt under 45 CFR 46.101(b), but covered by the HIPAA Privacy (and Security) Rules.
Similarities:	<ul style="list-style-type: none"> • Many entities that conduct research involving repositories of human biological materials are covered by more than one of these regulations.

Concept	Identifiable information
HHS OHRP Human Subjects Regulations 45 CFR 46	<ul style="list-style-type: none"> • The HHS regulations define human subject as: “a living individual about whom an investigator (whether professional or student) obtains... identifiable private information.” • The regulations state further that “Privacy information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects. [Emphasis added] (See 45 CFR 46.102(f)) • The HHS Office for Human Research Protections (OHRP) does not consider research involving only coded private information or specimens to involve human subjects as defined under 45 CFR 46.102(f) if the following conditions are both met: <ul style="list-style-type: none"> 1) the private information of specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and 2) the investigators(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example: <ul style="list-style-type: none"> (a) a key to decipher the code is destroyed before the research begins; (b) the investigators and the holder of the individual identifiers enter into an agreement prohibiting the release of individual identifiers to the investigators under any circumstances, until the individuals are deceased; (c) there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of individual identifiers to the investigators under any circumstances, until

²⁴ http://privacyruleandresearch.nih.gov/research_repositories.asp

	<p>the individuals are deceased; or (d) there are other legal requirements prohibiting the release of individual identifiers to the investigators, until the individuals are deceased.</p>
<p>HHS FDA Human Subjects Regulations 21 CFR 50, 56 & 812</p>	<ul style="list-style-type: none"> • Title 21 CFR parts 50, 56, and 812 do not directly address or define individually identifiable health information. • However, 21 CFR §50.50.25(a)(5) requires, in seeking informed consent, the subject to be provided with “A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the FDA may inspect the records.” • 21 CFR §56.111(a)(7) directs the IRB to determine that “Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
<p>HHS Privacy Rule 45 CFR 160 & 164 subparts A & e</p>	<ul style="list-style-type: none"> • Individually Identifiable Health Information – subset of health information, created or received by a covered entity or employer and relates to past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present or future payment for provision of health, and that identifies the individual or there is a reasonable basis to believe the information can be used to identify the individual. NB: includes information about decedents. • De-identified information – 2 Methods: (i) statistician determines that “risk is very small that information could be used, alone or in combination with other reasonably available information, by an anticipated recipient to identify an individual; and (ii) “Safe Harbor Method” – removal of 18 identifiers. See §160.514(b)(2) for list of identifiers. NB: 1. Codes or keys are permitted if they are not derived from information about the individual, are not capable of being translated so as to identify the individual, and the covered entity does not use or disclose the code or other means of record identification for any purpose and does not disclose the mechanism for re-identification. 2. Covered Entity does not have actual knowledge that the information could be used alone or in combination with other information to identify an individual who is the subject of the information. • Limited Data Set – Permits more data elements than the de-identification standard. See §514(e) for list of prohibited identifiers. Limited Data Sets may include dates, city, town, state and zip code. Limited Data Sets may be used only for research, public health, or health care operations. Requires a data use agreement with the party to whom the Limited Data Set will be disclosed. • NB: Business associates may be engaged for the purpose of de-identifying data and/or creating a limited data set. Once either is created, the business associate may use the subsequently created de-identified information for any purpose, and pursuant to a data use agreement may only use the limited data set for research, public health

	or health care operations.
Significant Differences:	<ul style="list-style-type: none"> • The HIPAA Privacy and Security Rules have a more expansive definition of individually identifiable information than the HHS regulations. Due to this difference, some information that would be individually identifiable under the Privacy Rule would not be individually identifiable under the HHS regulations. • For example, under the HHS regulations, a limited data set under the HIPAA Privacy Rule would not be individually identifiable if the investigators cannot readily ascertain the identity of the individual(s) to whom the information or specimens pertains. • In addition, in contrast to the Privacy Rule, information that is linked with a code derived from individual identifiers or related to information about the individual is not considered to be individually identifiable under the HHS regulations if the investigators cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertains. Therefore, some coded information, in which a code has been derived from an individual identifier linked to or related to the individual, would be individually identifiable under the HIPAA Privacy Rule, but might not be individually identifiable under 45 CFR part 46. • Unlike the HHS regulations, the HIPAA Privacy (and Security Rule) also pertains to individually identifiable information about decedents. • Individually identifiable information is not addressed in the FDA regulations. Specifically, FDA’s definitions of human subject and subject do not contain a reference to individually identifiable information (see definition of human subject and subject below). Therefore, even research or clinical investigations involving anonymous information or specimens may be subject to FDA’s regulations.
Similarities:	<ul style="list-style-type: none"> • Some information that is individually identifiable under the HHS regulations is also individually identifiable under the HIPAA Privacy (and Security) Rules.

Concept	Research
HHS OHRP Human Subjects Regulations 45 CFR 46	<ul style="list-style-type: none"> • “<i>Research</i> means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes...” [See 45 CFR 46.102(d)]
HHS FDA Human Subjects Regulations 21 CFR 50, 56 &	<ul style="list-style-type: none"> • Research is not defined in the FDA regulations. However, FDA’s definition of “clinical investigation” at 21 CFR §56.102(c) concludes with the statement that “The terms <i>research</i>, <i>clinical research</i>, <i>clinical study</i>, <i>study</i>, and <i>clinical investigation</i> are deemed to be synonymous

812	<p>for purposes of this part.”</p> <ul style="list-style-type: none"> Also, 21 CFR §812.3(h) defines an “Investigation” to mean “...a clinical investigation <i>or research</i> involving one or more subjects to determine the safety or effectiveness of a device.” [Emphasis added.]
HHS Privacy Rule 45 CFR 160 & 164 subparts A & e	<ul style="list-style-type: none"> Defined at 45 CFR §160.501. Under HIPAA, “research” means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Follows Common Rule definition. HIPAA permits disclosures of individually identifiable health information for research through a number of pathways: <ol style="list-style-type: none"> For certain kinds of research relating to health care operations/quality of care, pursuant to a business associate agreement. De-identifying information Limited Data Set with a Data Use Agreement Pursuant to an Authorization (see below) Pursuant to a waiver of authorization by an IRB or Privacy Board (see below). Review preparatory to research (Note: See http://privacyruleandresearch.nih.gov/clin_research.asp for discussion of differences between HIPAA and Common Rule, and flexibility under HIPAA to recruit research subjects/tissue, including hiring a business associate to assist). See also Bernstein, 2004 Good Clinical Practice Journal, at 23 (June, 2004) for analysis of subject recruitment issues under HIPAA. Research on decedent’s information .
Significant Differences:	<ul style="list-style-type: none"> Under the HHS regulations and the Privacy Rule, the intent to develop or contribute to generalizable knowledge is key to whether the activity is research. In contrast, under the FDA regulations, the objective to generate data/information to be submitted to FDA or be available for FDA inspection is key to whether the activity is research. Not all activities that meet the definition of research under the HHS regulations and the HIPAA Privacy and Security Rules would meet FDA’s definition of a clinical investigation. Similarly, not all activities that meet FDA’s definition of a clinical investigation would meet the definition of research under the HHS regulations and the HIPAA Privacy and Security Rules.
Similarities:	<ul style="list-style-type: none"> Some activities involving repositories and human biological specimens will meet the relevant regulatory definitions of both a clinical investigation and research.

Concept	Clinical Investigation
HHS OHRP Human Subjects Regulations 45 CFR 46	<ul style="list-style-type: none"> • The HHS regulations do not contain the term, “clinical investigation.”
HHS FDA Human Subjects Regulations 21 CFR 50, 56 & 812	<ul style="list-style-type: none"> • Clinical investigation means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under §505(i), 507(d), or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that must meet the provisions of part 58, regarding non-clinical laboratory studies. The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part. (See 21 CFR §§50.3(c) and 56.102(c))
HHS Privacy Rule 45 CFR 160 & 164 subparts A & e	<ul style="list-style-type: none"> • No real differentiation between clinical investigation and treatment within research context. If individually identifiable health information is obtained by a covered entity, Privacy Rule applies
Significant Differences:	<ul style="list-style-type: none"> • Under the HHS regulations and the Privacy Rule, the intent to develop or contribute to generalizable knowledge is key to whether the activity is research. • In contrast, under the FDA regulations, the objective to generate data/information to be submitted to FDA or be available for FDA inspection is key to whether the activity is research. • Not all activities that meet the definition of research under the HHS regulations and the HIPAA Privacy and Security Rules would meet FDA’s definition of a clinical investigation. • Similarly, not all activities that meet FDA’s definition of a clinical investigation would meet the definition of research under the HHS regulations and the HIPAA Privacy and Security Rules.
Similarities:	<ul style="list-style-type: none"> • Some activities involving repositories and human biological specimens will meet the relevant regulatory definitions of both a clinical investigation and research.

Concept	Human Subject
HHS OHRP Human Subjects Regulations 45 CFR 46	<ul style="list-style-type: none"> The HHS regulations state, “<i>Human subject</i> means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual or (2) identifiable private information...” (See 45 CFR 46.102(f))
HHS FDA Human Subjects Regulations 21 CFR 50, 56 & 812	<ul style="list-style-type: none"> Human subject means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient. (See 21 CFR 50.3(g) and 56.102(e)) Note that “Subject” is defined differently in 21 CFR part 812.
HHS Privacy Rule 45 CFR 160 & 164 subparts A & e	<ul style="list-style-type: none"> Does not address human subjects per se. Addresses individually identifiable health information of an individual. Flexibility on obtaining information about decedents if only used for research.
Significant Differences:	<ul style="list-style-type: none"> See discussion of “Identifiable Information” above. Also, unlike the HHS regulations, the FDA regulations refer to a recipient or user of the FDA regulated product, control, or specimen. An individual may be a human subject under HHS regulations and not under the FDA’s regulations. Similarly, an individual may be a human subject under the FDA regulations and not under the HHS regulations
Similarities:	<ul style="list-style-type: none"> See discussion of “Identifiable Information” above. Some individuals will be human subjects under both HHS’ and FDA’s regulations.

Concept	Subject
HHS OHRP Human Subjects Regulations 45 CFR 46	<ul style="list-style-type: none"> The HHS regulations do not define “subject.”
HHS FDA Human Subjects Regulations 21 CFR 50, 56 & 812	<ul style="list-style-type: none"> Subject means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease. (See 21 CFR §812.3(p)) <u>Note</u>: The preamble of 21 CFR part 812 (45 FR 3741, January 18, 1980) suggests that no difference in scope was intended between 21 CFR part 812 and parts 50 and 56 with respect to this definition.
HHS Privacy Rule 45 CFR 160 & 164 subparts A & e	<ul style="list-style-type: none"> Does not address human subjects per se. Addresses individually identifiable health information of an individual. Flexibility on obtaining information about decedents if only used for research.
Significant Differences:	<ul style="list-style-type: none"> Same as above.
Similarities:	<ul style="list-style-type: none"> See discussion of “Identifiable Information” above.

Concept	IRB/Privacy Board Responsibilities/Review
<p>HHS OHRP Human Subjects Regulations 45 CFR 46</p>	<ul style="list-style-type: none"> • Before non-exempt human subjects research may be conducted or supported by HHS, the HHS regulations require that such research be reviewed and approved by an IRB meeting the membership requirements of 45 CFR 46.107. • IRB review of human subjects research must meet the requirements of 45 CFR 46.109, which includes among other things, that the IRB conduct continuing review of human subjects research at intervals appropriate to the degree of risk, but not less than once per year. • In addition, the HHS regulations permit expedited review procedures for certain kinds of human subjects research that have been found by an IRB to involve no more than minimal risk to research subjects, or for minor changes in previously IRB-approved research during the period (of one year or less) for which approval is authorized. An expedited review procedure consists of a review of research involving human subjects by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB in accordance with the requirements at 45 CFR 46.110. See the following URL for a list of categories of research that may be reviewed by the IRB through an expedited review procedure: http://www.hhs.gov/ohrp/humansubjects/guidance/expedited98.htm. • The following category of expedited review is typically most relevant to research involving repositories and human biological specimens: “Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)”
<p>HHS FDA Human Subjects Regulations 21 CFR 50, 56 & 812</p>	<ul style="list-style-type: none"> • FDA requires any clinical investigation that meets the requirements for submission to FDA, cannot be initiated unless it has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of Part 56. Note: the following categories of research are exempt from the requirements for IRB review: <ul style="list-style-type: none"> • Any investigation that began before July 27, 1981 and was subject to IRB review requirements that conformed to FDA requirements in effect at that time. • Any investigation that began before July 27, 1981 and was not subject to IRB review requirements under FDA regulations before that date. • Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review. • In addition, on the application of a sponsor or sponsor-investigator, the FDA may waive any of the requirements contained in Part 56, including the requirement of IRB review, for specific research

	<p>activities or for classes of research activities otherwise covered by Part 56. (See 21 CFR §§56.104 and 56.105.) However, §520(g)(3)(A) of the act requires meaningful IRB review and approval, so complete waiver of IRB review and approval is not permitted for device studies. – see §520(g)(3)(A) of the act.</p> <ul style="list-style-type: none"> • FDA and HHS simultaneously published identical lists of categories of research that may be reviewed by the IRB through an expedited review procedure. (See 63 FR 60353, November 9, 1998, for FDA’s list.) • An IRB may use the expedited review procedure to review either or both of the following: (1) Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk, (2) minor changes in previously approved research during the period (of 1 year or less) for which approval is authorized. See 21 CFR §56.110. • Note: The FDA and HHS expedited review regulations, procedures, and lists are virtually identical.
<p>HHS Privacy Rule 45 CFR 160 & 164 subparts A & e</p>	<ul style="list-style-type: none"> • Only responsible for evaluating and granting waivers of authorization. Under the Privacy Rule itself, neither IRBs nor Privacy Boards have any affirmative responsibility for approving forms of authorization or any other aspect of research, other than a waiver or alteration of authorization. See 68 Federal Register at 63110 (November 7, 2003) and Letter from Richard Campanelli, Director, Office for Civil Rights to Mr. Stan Crosley, Chief Privacy Officer, Eli Lilly & Company (April 15, 2003). See also http://privacyruleandresearch.nih.gov/privacy_boards_hipaa_privacy_rule.asp for HHS discussion of privacy boards. • See also 45 CFR 164.512(i)(1)(i)(B) for composition requirements of a privacy board
<p>Significant Differences:</p>	<ul style="list-style-type: none"> • In general, under the HHS and FDA regulations, the informed consent document/process must be reviewed and approved by an IRB before human subjects research/a clinical investigation may begin. • In contrast, the Privacy Rule never requires that Authorization language to use or disclose protected health information for research purposes be reviewed and approved by an IRB or Privacy Board. • IRB composition and quorum requirements differ between HIPAA Privacy Rule, and HHS and FDA regulations. • While HHS and FDA regulations do not permit the use of expedited review to disapprove research, the HIPAA Privacy Rule does permit the use of expedited review to disapprove a waiver of authorization to use or disclose protected health information for research purposes.
<p>Similarities:</p>	<ul style="list-style-type: none"> • All regulations permit expedited IRB (or, under the Privacy Rule, Privacy Board) review for certain minimal risk research.

Concept	Informed Consent/Authorization for Research
HHS OHRP Human Subjects Regulations 45 CFR 46	<ul style="list-style-type: none"> • No investigator may involve a human being as a subject in research covered by 45 CFR part 46 without the legally effective informed consent of the subject or the subject’s legally authorized representative, unless an IRB has waived or altered the required elements for informed as permitted at 45 CFR 46.116 (c) or (d). <u>The following are the basic elements of informed consent:</u> <ol style="list-style-type: none"> 1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject’s participation, a description of the procedures to be followed, and identification of any procedures which are experimental; 2. a description of any reasonably foreseeable risks or discomforts to the subject; 3. a description of nay benefits to the subject or to others which may reasonably be expected from the research; 4. a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject; 5. a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained; 6. for research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained; 7. an explanation of whom to contact for answers to pertinent questions about the research and research subjects’ rights, and whom to contact in the event of a research-related injury to the subject; and 8. a statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
HHS FDA Human Subjects Regulations 21 CFR 50, 56 & 812	<ul style="list-style-type: none"> • No investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject’s legally authorized representative. (See 21 CFR §50.20.) • Limited emergency exceptions must be embodied in regulations, and must be consistent with §520(g)(3)(D), which requires that the investigator determine in writing that there exists a life-threatening situation involving the human subject of such testing which necessitate the use of such device and it is not feasible to obtain informed consent from the subject and there is not sufficient time to obtain such consent from his representative. An independent physician must concur unless immediate use of the device is required to save the life of the human subject of such testing and there is not sufficient time to obtain such concurrence. • Regulations interpreting these emergency exceptions are:

	<p>Exceptions from general requirements of informed consent (§50.23), which applies on a patient-by-patient basis, and Exception from informed consent requirements for emergency research (§50.24), that applies to a limited class of research studies meeting certain specific requirements. [Note that HHS published a comparable Secretarial waiver for research meeting the criteria of this rule; see 61 FR 51531, October 2, 1996.] (Note: Neither of the above exceptions (or the regulation below) would be applicable to the type of research being discussed.)</p> <ul style="list-style-type: none"> • Additionally, FDA has criteria that can be applied by the President in waiving the prior consent requirement for the administration of an investigational new drug to a member of the armed forces in connection with the member's participation in a particular military operation. See 21 CFR §50.23(d)
<p>HHS Privacy Rule 45 CFR 160 & 164 subparts A & e</p>	<ul style="list-style-type: none"> • A HIPAA authorization must include: <ol style="list-style-type: none"> 1. Description of the information to be used or disclosed that identifies the information in a specific and meaningful fashion. 2. The name or other specific identification of the person(s), or class of persons, authorized to make the requested use of disclosure. 3. The name or other specific identification of the person(s), or class of persons, to whom the covered entity may make the requested use or disclosure. 4. A description of each purpose of the requested use or disclosure. 5. An expiration date or an expiration event that relates to the individual or the purpose of the use or disclosure (“end of the research study,” “none,” or similar language if for research, including the creation and maintenance of a research database or research repository. 6. Signature of the individual and date. • Must also contain statements adequate to put the individual on notice of their (i) right to revoke the authorization, the exceptions to this right (or a reference to the notice of privacy practices where the limitation is stated); (ii) the ability or inability to condition treatment on the authorization (note: may preclude participation in the research if individual is unwilling to sign authorization); (iii) the potential for re-disclosure by the recipient. Must also be in plain language and a copy provided to the individual. • See http://privacyruleandresearch.nih.gov/authorization.asp for NIH discussion of HIPAA authorization and sample. • See also http://privacyruleandresearch.nih.gov/pdf/research_repositories_final.pdf for 2-step process associated with tissue harvesting and subsequent disclosure for research. The section beginning at ‘5’ includes important commentary indicating that a reference to the banking of tissue may be a specific enough description of the purpose of the use so long as appropriate disclosure is made for the research use when the tissue is withdrawn from the bank. Prudence would dictate that the authorization also note that various researchers will be withdrawing tissues for a variety of research purposes.
<p>Significant Differences:</p>	<ul style="list-style-type: none"> • The elements for informed consent under the HHS and FDA regulations address the research as a whole, not just the use and disclosure of individually

	<p>identifiable health information as is the case with the Privacy Rule.</p> <ul style="list-style-type: none"> • Under certain limited circumstances, the HHS and FDA regulations permit an IRB-approved informed consent to be broader than for a specific research study. For example, when obtaining biological or tissue specimens from living individuals to create a repository established and maintained for research purposes, the IRB-approved informed consent document may include a description of the specific types of research to be conducted using the data and specimens maintained for the repository. In addition, for future research that involves the study of individually identifiable information maintained for the repository, an IRB may determine that the original informed consent for the creation of the repository satisfies the requirements of 45 CFR part 46 and/or 21 CFR part 50 for the conduct of future research, provided that the future research now being proposed was adequately described in the original informed consent. For some tissue repositories, the specific type of research that may be done in the future on collected biological and tissue specimens was unknown when the tissue was collected but sufficiently anticipated and described to satisfy 45 CFR part 46 or 21 CFR part 50. However, the informed consent information describing the nature and purposes of the research should be as specific as possible. • In contrast, under the HIPAA Privacy Rule, an Authorization, whether combined with an IRB-approved consent or separate, can not be for future unspecified research. Rather, the Authorization would need to describe the research purpose of the use or disclosure of protected health information, required by 45 CFR 164.508, which must be research trial or study specific. Even where an Authorization is combined with an IRB-approved informed consent, the Authorization would need to be limited in such a way, even though the HHS and FDA regulations would permit the IRB-approved informed consent document to also describe the certain unspecified types of research that may be conducted in the future using the data and specimens maintained for the repository. Thus, uses and disclosures of protected health information for such future research would require an additional Authorization, except as permitted without Authorization, under section 164.512(i) (e.g., with a waiver of Authorization) or 164.514(e) (i.e., as a limited data set with a data use agreement).
<p>Similarities:</p>	<ul style="list-style-type: none"> • All of the regulations permit Authorization language to be combined with an informed consent document under specified circumstances. • Both the HHS regulations and the Privacy Rule define “research” in such a way that the creation of a research repository can be considered to be a research study, even when the specific future research to be conducted using specimens/data from the repository are not known at the time the tissue and data are deposited. <p>Therefore, under the Privacy Rule, a description of the research repository would meet the Authorization requirement for a “description of each purpose of the requested use or disclosure.” Future use or disclosure of PHI from the research repository would require another Authorization, except as permitted without Authorization, under section 164.512(i) (e.g., with a waiver of</p>

	<p>Authorization) or 164.514(e) (i.e., as a limited data set with a data use agreement).</p> <ul style="list-style-type: none"> • Similarly, under the HHS regulations, the informed consent document and process would provide information about research study; i.e. the research repository. Future human subjects research using identifiable private information from the repository would require informed consent or a waiver of informed consent under 45 CFR 46.116. However, an IRB may determine that the original informed consent for the creation of the repository satisfies the requirements of 45 CFR part 46 and/or 21 CFR part 50 for the conduct of future research, provided that the future research now being proposed was adequately described in the original informed consent
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Concept	Waiver of Informed Consent/Exception to Authorization for Research
<p>HHS OHRP Human Subjects Regulations 45 CFR 46</p>	<ul style="list-style-type: none"> • Under 45 CFR 46.116 (c) and (d) and IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent or waive the requirement to obtain informed consent provided the IRB finds and documents specified criteria. • Under 45 CFR 46.116 (c) and (d) and IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent or waive the requirement to obtain informed consent provided the IRB finds and documents specified criteria. • The criteria specified at 45 CFR 46.116(d) are: <ol style="list-style-type: none"> 1. the research involves no more than minimal risk to the subjects; 2. the waiver or alteration will not adversely affect the rights and welfare of the subjects; 3. the research could not practicably be carried out without the waiver or alteration; and 4. whenever appropriate, the subjects will be provided with additional pertinent information after participation. • The criteria specified at 45 CFR 46(c) are: <ol style="list-style-type: none"> 1. the research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and 2. the research could not practicably be carried out without the waiver or alteration. • The IRB, for some or all subjects, may waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds either (1) that the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject to the research,

	<p>and the subject's wishes will govern; or</p> <ul style="list-style-type: none"> • (2) that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context. See 45 CFR 46.117(c).
<p>HHS FDA Human Subjects Regulations 21 CFR 50, 56 & 812</p>	<ul style="list-style-type: none"> • FDA allows the IRB, for some or all subjects, to waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context. See 21 CFR §56.109(c)(1).
<p>HHS Privacy Rule 45 CFR 160 & 164 subparts A & e</p>	<ul style="list-style-type: none"> • Parallels Common Rule, but focuses instead on minimal risk to privacy as opposed to minimal risk of physical harm under the Common Rule. As noted above, either an IRB or a Privacy Board may provide a waiver or alteration of authorization. Documentation of a waiver must include: <ol style="list-style-type: none"> 1. A statement identifying the IRB or privacy board and the date the waiver or alteration was approved. 2. Waiver Criteria: A statement by the IRB or privacy board that it has determined: (a) the use or disclosure of PHI involves no more than minimal risk to the privacy of individuals based on, at least, the presence of the following elements: (i) an adequate plan to protect the identifiers from improper use and disclosure; (ii) an adequate plan to destroy the identifiers at the earliest opportunity consistent with the conduct of research, unless there is a justification for retaining the identifiers or such retention is otherwise required by law; and (iii) adequate written assurances that the PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the study, or for other research for which the use or disclosure of the PHI is permitted under the Privacy Rule; (b) The research could not practicably be conducted without a waiver or alteration; and (c) The research could not practicably be conducted without access to and use of the PHI. 3. A brief description of the PHI for which use or access has been determined to be necessary by the IRB or privacy board. 4. A statement that the waiver or alteration has been reviewed or approved under either normal or expedited review procedures, in the case of an IRB pursuant to the Common Rule, and in the case of a privacy board subject to certain procedures that parallel the Common Rule (see 45 CFR §164.512(i)(2)(iv)(B) and (C)). 5. Documentation of the alteration or waiver must be signed by the chair or other member of the IRB or privacy board. • HIPAA also requires a Covered Entity to account to patients for disclosures made for research pursuant to a waiver of authorization.
<p>Significant Differences:</p>	<ul style="list-style-type: none"> • Unlike the HHS regulations, the FDA regulations do not provide for a waiver of informed consent that would be applicable to research involving repositories or human biological specimens. • Criteria for the waiver of Authorization are privacy specific, whereas the

	<p>criteria for the waiver of informed consent focus more broadly on the research study as a whole.</p> <ul style="list-style-type: none"> • The HHS and FDA regulations permit documentation of informed consent to be waived under certain conditions. It is unclear whether the HIPAA Privacy Rule would permit documentation of Authorization to be waived. • Unlike the HIPAA Privacy Rule, there is no requirement for “accounting for disclosures” under the HHS or FDA regulations
Similarities:	<ul style="list-style-type: none"> • The waiver criteria under both the HHS regulations and the HIPAA Privacy Rule are similar and compatible. • FDA and HHS regulations both permit an IRB to waive the requirement to obtain a signed informed consent document if specified conditions are met.

Concept	Returning Research Results to Subjects²⁵
HHS OHRP Human Subjects Regulations 45 CFR 46	<ul style="list-style-type: none"> • Not addressed directly in 45 CFR part 46. However, OHRP has provided the following guidance on the disclosure of research findings: <ul style="list-style-type: none"> • Where appropriate, the IRB may find that the informed consent document/process should include: <ul style="list-style-type: none"> • A statement regarding subjects’ access to information learned from the research, if they so choose. • A statement about the investigator’s policy regarding disclosure of interim results and/or incidental findings from the research • A statement regarding third party (family members, physicians, employers, insurance companies) access to research data
HHS FDA Human Subjects Regulations 21 CFR 50, 56 & 812	<ul style="list-style-type: none"> • Not addressed directly by FDA regulations.
HHS Privacy Rule 45 CFR 160 & 164 subparts A & e	<ul style="list-style-type: none"> • The HIPAA Privacy Rule affords individuals a right to inspect and obtain a copy of their PHI held by covered entities in a “designated record set.” A designated record set includes any record that is maintained by the covered entity or its business associate that is a medical, billing, enrollment, or payment record or other record that is used to make decisions about the subject of the information. • Covered entities are required to have policies and procedures for responding to access requests, and researchers that are workforce members of a covered

²⁵ CLIA, 42 U.S.C. 263a, and the accompanying regulations, 42 CFR part 493, require clinical laboratories to comply with standards regarding the testing of human specimens. CLIA regulations exempt the components or functions of “research laboratories that test human specimens but do not report patient-specific results for the diagnosis, prevention or treatment of any disease or impairment of, or the assessment of the health of individual patients.” However, laboratories that are subject to CLIA must disclose test results or reports only to “authorized persons,” as defined by state law. If a state does not define “authorized persons,” federal law defines the term as the person who orders the test.

	<p>entity may wish to coordinate any response to a subject’s request with the medical records department, privacy officer, or legal counsel to ensure compliance with both the Privacy Rule and institutional policies.</p> <p><u>Exceptions to Rights of Access:</u></p> <ul style="list-style-type: none"> • In some cases research data may not be considered part of the designated record set if, for example, the research data is not used to make decisions about the individual and is not part of the medical record. In that case, the individual would not have a right to access the data, but this should be examined on a case-by-case basis with institutional officials. • In the case of research that includes treatment, including clinical trials, the Privacy Rule permits a covered entity to suspend the individuals’ access rights until the end of the research study, provided the individual agreed to the suspension when consenting to participate in the research and was informed that right of access would be reinstated upon completion of the research. The Privacy Rule permits the covered entity to insert in the Authorization form a statement by which the subject agrees to the suspension of the right to access during the clinical trial and that informs the individual of that the right to access will be reinstated upon completion of the research. (See HHS guidance, Clinical Research and the HIPAA Privacy Rule, page 15²⁶) • The Privacy Rule creates 2 CLIA-related exceptions to individuals’ general right of access to PHI held in a designated record set: (1) Covered entities maintaining PHI that is subject to CLIA requirements do not have to provide individuals with a right of access to or a right to inspect and obtain a copy of this information if the disclosure of the information to the individual would be prohibited by CLIA (see 45 CFR 164.524(1)(iii); and (2) Covered entities that are exempt from CLIA under the following exemption are also excluded from the Privacy Rule’s access requirement: CLIA regulations exempt the components or functions of “research laboratories that test human specimens but do not report patient specific results for the diagnosis, prevention or treatment of any disease or impairment of, or the assessment of the health of individual patients.”
Significant Differences:	<ul style="list-style-type: none"> • Neither the Common Rule nor FDA regulations directly address return of research results. OHRP does have guidelines for including provisions for access in consent documents. The Privacy Rule requires access by an individual to PHI held by the covered entity, but specifies conditions under which the right of access would not apply.
Similarities:	<ul style="list-style-type: none"> • None of the regulations specifically addresses return of research results.

²⁶ http://privacypolicyandresearch.nih.gov/pdf/clin_research.pdf

Concept	Other Definitions
HHS OHRP Human Subjects Regulations 45 CFR 46	<ul style="list-style-type: none"> • Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. (See 45 CFR 46.102(i))
HHS FDA Human Subjects Regulations 21 CFR 50, 56 & 812	<ul style="list-style-type: none"> • Minimal risk means that the risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. (See 21 CFR §50.3(l) and §56.102(i))
HHS Privacy Rule 45 CFR 160 & 164 subparts A & e	<ul style="list-style-type: none"> • Protected health information: is individually identifiable health information (see above) that is transmitted by electronic media; maintained in electronic media; or transmitted in any other form or medium (excluding certain education records and other records that are protected by the Family Educational Rights and Privacy Act (FERPA)). • Covered Entity: a health plan, a health care clearinghouse, or a health care provider who conducts transmits any health information in electronic form in connection with a HIPAA standard transaction. • Individually identifiable health information: See above. • Use: with respect to individually identifiable health information, the sharing, employment, application, <i>utilization, examination, or analysis</i> of such information within in an entity that maintains such information. • Disclosure: the release, transfer, provision of, access to, or divulging in any other manner of information outside the entity holding the information. • Privacy Board: See discussion above.
Significant Differences:	<ul style="list-style-type: none"> • The Privacy Rule defines terms not used by the FDA or the Common Rule.
Similarities:	<ul style="list-style-type: none"> • Minimal risk is defined similarly in the FDA regulations and the Common Rule.

Concept	Guidance
HHS OHRP Human Subjects Regulations 45 CFR 46	<ol style="list-style-type: none"> 1. OHRP guidance on research repositories and databases: http://www.hhs.gov/ohrp/humansubjects/guidance/reposit.htm 2. OHRP guidance regarding research on human embryonic stem cells, germ cells and stem cell-derived test articles: http://www.hhs.gov/ohrp/policy/index.html#stem 3. OHRP guidance on informed consent: http://www.hhs.gov/ohrp/policy/index.html#informed 4. OHRP Guidance on Research Involving Coded Private Information or Biological Specimens: http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf 5. OHRP Guidance on Engagement in Research (1999)

	http://www.hhs.gov/ohrp/humansubjects/assurance/engage.htm
HHS FDA Human Subjects Regulations 21 CFR 50, 56 & 812	<ul style="list-style-type: none"> FDA’s guidance documents, including information sheets, on a variety of topics that deal with human subject protection and good clinical practice are available on Internet at http://www.fda.gov/oc/gcp/guidance.html Only one of these explicitly addresses human biological specimens: Guidance on Informed Consent for <i>In Vitro</i> Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable http://www.fda.gov/cdrh/oivd/guidance/1588.html
HHS Privacy Rule 45 CFR 160 & 164 subparts A & e	<ol style="list-style-type: none"> Office for Civil Rights Fact Sheet for Research²⁷ National Institutes of Health, Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule (9/25/03). National Institutes of Health, Clinical Research and the HIPAA Privacy Rule²⁸ National Institutes of Health, Research Repositories, Databases, and the HIPAA Privacy Rule,²⁹ National Institutes of Health, Privacy Boards and the HIPAA Privacy Rule,³⁰

Note: The comparisons provided in this table are based on the authors understanding and interpretation of existing regulatory guidance. The table does not in and of itself constitute official policy.

²⁷ <http://www.hhs.gov/ocr/hipaa/guidelines/research.pdf> (12/3/02, revised 4/3/03)

²⁸ http://privacyruleandresearch.nih.gov/pdf/clin_research.pdf (February 5, 2004).

²⁹ http://privacyruleandresearch.nih.gov/pdf/research_repositories_final.pdf (1/23/04).

³⁰ http://privacyruleandresearch.nih.gov/pdf/privacy_boards_hipaa_privacy_rule.pdf (9/30/03)

Tool B

Common Rule Specific Issues

The following questions and answers were developed to address areas that have sometimes led to confusion on the part of researchers and IRB members about the applicability of the Common Rule to specific situations related to use of human specimens and data for research.

Specimen Banking:

When is operating a Human Specimen Bank considered research?

Both the Common Rule and the FDA regulations consider the activity of creating and maintaining a specimen bank for research purposes to be a research activity. Operationally, that means that specimen repositories that either involve interaction or intervention with the subject to obtain the specimens or that record and maintain identifying information associated with the specimens should develop a protocol for their operations and submit that to an IRB for approval.

Is informed consent required to collect a specimen?

Generally, informed consent is required for the collection of specimens for research. However, as described further below, there are circumstances where consent may not be required. In all cases, an IRB or designated institutional official who is not engaged in the research should make the final decision about what regulatory requirements apply.

If informed consent is required, what must it include?

The informed consent should include:

- Details about the type of specimen and how it will be obtained from the person, whether as a part of routine care, or specifically for research. Any associated risks must be clearly described.
- Whether or not any identifying information will be retained with the specimen
- How the specimen will be used:
 - Will the specimen be:
 - Used for a single research protocol?
 - Used for multiple protocols
 - Placed into a tissue bank for future use
 - Who will have access to the specimen:
- If the specimen is placed in a bank, how does that bank operate?
- How to withdraw one's specimen from the research/bank.
- Whether or not the tissue source will be recontacted in the future – and for what reasons.

When is waiver of informed consent appropriate?

Waiver of consent is appropriate when the research is minimal risk and the IRB determines that it meets all of the other requirements for waiver of consent. In assessing risks, it is important to consider the privacy and confidentiality

protections in place and mechanisms for the oversight of the repository. In addition, it is also important to consider the risks of the research that will use the specimens and any oversight for the use of the specimens (e.g. review by an IRB of the specific research protocol for use of the specimens) (See Tool E for a discussion of risks).

Is the deposit of a specimen into a tissue bank considered research?

If the tissue bank supports research activities, then yes, the collection and placement of those specimens into a bank is considered to be part of the research process.

What should be included in the IRB review of a specimen resource?

Repository protocols should provide enough information to allow an IRB to assess compliance with the federal human subjects regulations (45 CFR 46), relevant medical records and privacy legislation, and state and local laws. The amount of information and level of detail required will vary depending upon the size of the repository, the nature of the research and the identifiability of the persons from whom the specimens were collected. In cases where specimens are collected as part of a specific research project, it may be desirable to submit a separate protocol for the repository operation.

The tissue bank's rules of operation should specify how specimens can be accessed from the bank, and what regulatory oversight is appropriate. The IRB review of the tissue bank should include these specific procedures.

Before preparing their documentation, researchers should discuss their protocols with their IRB chair to determine IRB preferences and the specific requirements of your institution.

Use of Specimens:

When is using specimens from a human specimen bank considered human subjects research?

In general, whenever a researcher obtains an identifiable specimen from a tissue bank, this is human subjects research and requires an IRB review, an informed consent or a waiver of informed consent.

When is informed consent required for the specific research use of specimens obtained from a repository?

Informed consent is required whenever the specimens being accessed from the bank have identifiable information or when the proposed research use was not included in the consent obtained when the specimen was placed into the bank and the waiver criteria cannot be met. Some ethicists and patient advocates believe that all samples used in research should be used only with patient consent and advocate going beyond the requirements of the Common Rule to ensure that

consent is obtained. The final decision on whether or not to require consent in specific cases will depend on institutional policy and/or IRB practice.

When is waiver of consent for use of specimens appropriate?

Waiver of consent is allowed under the Common Rule whenever the research is minimal risk and meets the other requirements specified in the regulation. The requirements for waiver are: that the research involves minimal risk to subjects, the rights and welfare of the subjects would not be adversely effected, the research could not practicably be carried out without waiver and, whenever appropriate, subjects will be provided additional pertinent information after participating. The decision about whether or not to allow a waiver of informed consent is made by the IRB.

When is use of the specimen not subject to the Common Rule?

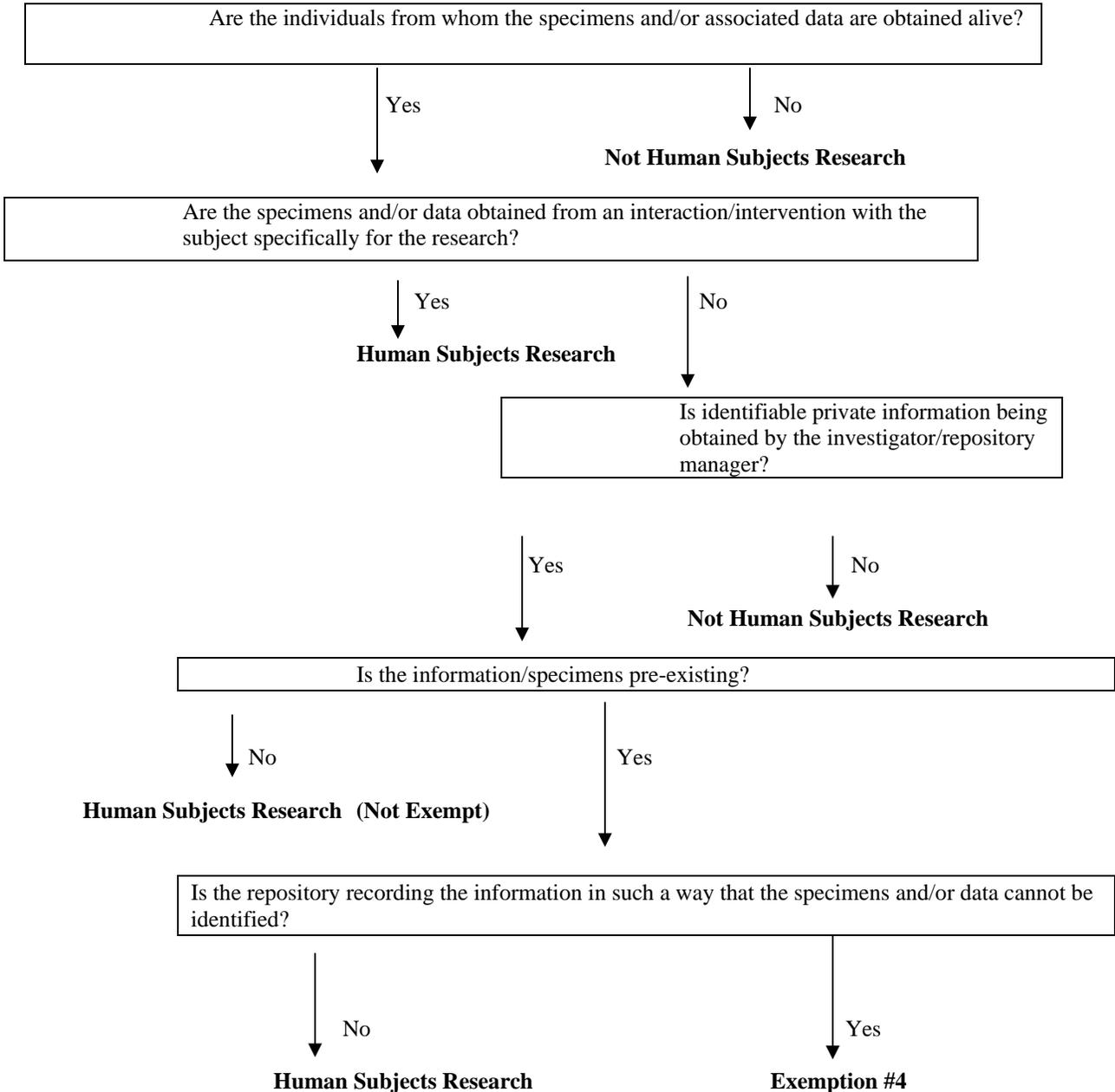
The OHRP *Guidance on Research Involving Coded Private Information or Biological Specimens*” (2004) addresses the question of when use of human specimens and data may not meet the definition of human subjects research according to 45 CFR part 46 and would not be covered by the regulation’s requirements.. Essentially the policy states that if 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 identity of the individual(s) to whom the coded private information or specimens pertain, it is not human subjects research under the Common Rule. The policy does describe some exceptions, however; for example, when the investigator collecting the specimens and information and the recipient investigator are part of the same research team.

The following flow charts can be used to help interpret how the Common Rule applies to collection and banking of specimens and associated data for research (Flowchart 1) and to research use of specimens (Flowchart 2)

Flowchart 1

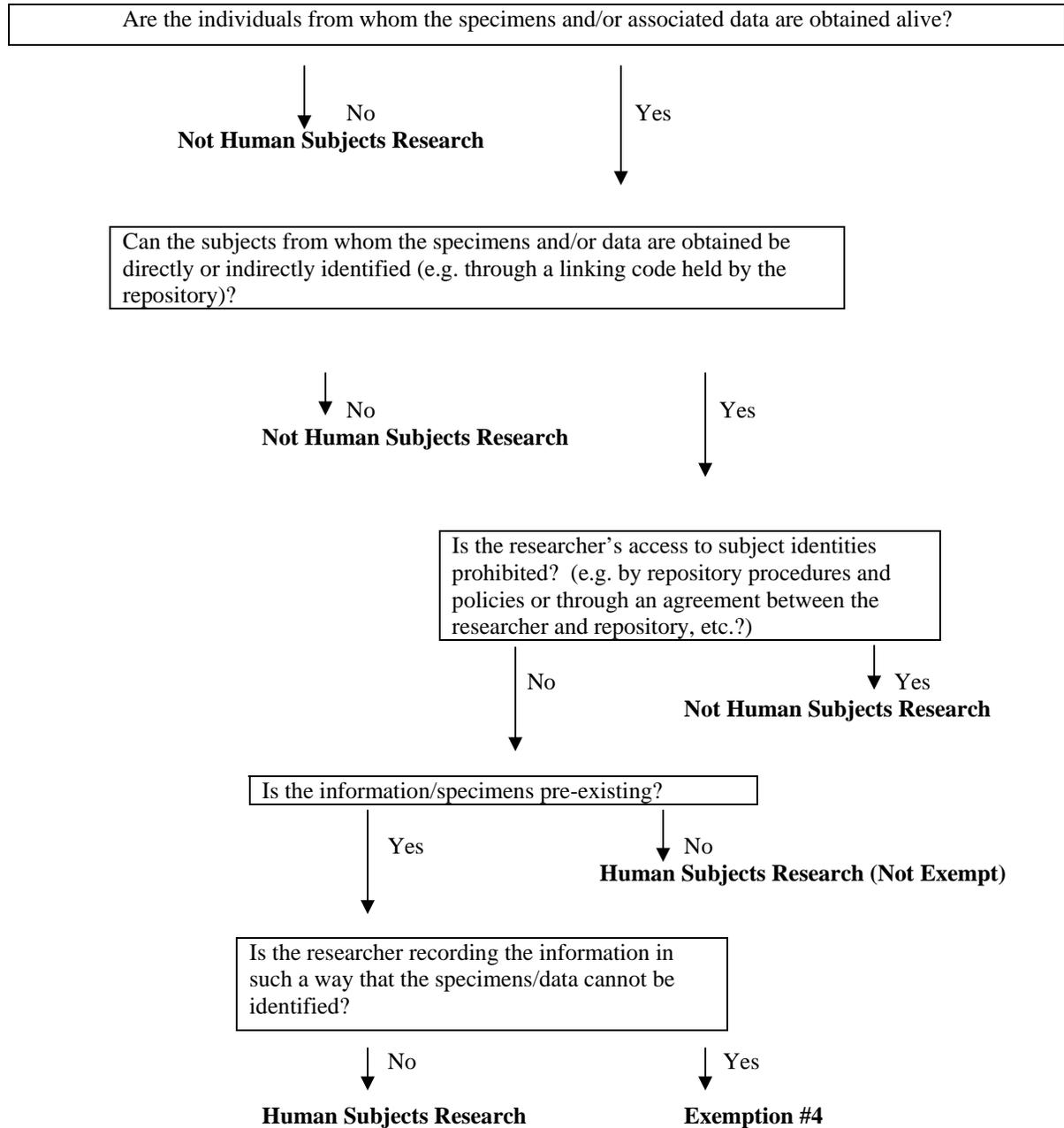
COLLECTION AND BANKING OF SPECIMENS AND/OR ASSOCIATED DATA FOR RESEARCH

This flowchart was designed to help illustrate when the collection and banking of specimens and/or associated data for research is considered human subject research under the HHS Human Subject Protection Regulations, 45 CFR part 46 (<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm>) and when it meets the criteria for Exemption #4 [45 CFR part 46.101(b)]. A second, companion flow chart (Flowchart 2) should be used for the research use of specimens and associated data obtained from a repository.



Flow Chart 2
RESEARCH USE OF SPECIMENS AND/OR ASSOCIATED DATA

This flowchart was designed to help illustrate when the research use of specimens and/or associated data is considered human subjects research under the HHS Human Subject Protection Regulations, 45 CFR part 46 (<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm>) and when it meets the criteria for Exemption #4 [45 CFR part 46.101(b)]. The preceding companion flowchart (Flowchart 1) should be used for evaluating the applicability of the Common Rule to collection and banking of specimens and/or associated data.



Tool C

How do FDA Regulations differ from the Common Rule?

The FDA human subjects regulations apply to any research that is conducted by the FDA or will result in a submission for pre-marketing approval from the FDA. The FDA regulatory requirements are generally the same as those of the Common Rule. However, there are some critical differences:

- Some key terms are defined differently, for instance the FDA's regulations on in vitro diagnostic devices defines a human subject simply as a specimen. The FDA's regulations don't specifically define research, but rather refer to clinical investigation and investigation.
- The FDA regulations do not allow waiver of consent except for emergency use. However, the FDA has recently issued guidance, "*Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable*" that indicates that the FDA will not enforce³¹ the requirement for informed consent for in vitro diagnostic device studies if all of the following elements are present:
 - The investigation meets the criteria for investigational device exemption (IDE)
 - the study uses leftover specimens (or from repositories or other research)
 - the specimens are not individually identifiable. (Coded specimens are not individually identifiable if no one associated with the investigation can link the specimen to the subject, directly or indirectly.),
 - specimens may be accompanied by clinical information if the information does not make the subjects identifiable, the patients' caregivers are different from and do not share information with researchers,
 - specimens are provided without identifiers and the supplier has established policies and procedures to prevent release of personal information, and
 - the study has been reviewed by an IRB.

These requirements are consistent with the OHRP *Guidance on Research Involving Coded Private Information or Biological Specimens*" (2004)

³¹ "...FDA intends to exercise enforcement discretion, under certain circumstances, with respect to its current regulations governing the requirement for informed consent when human specimens are used for FDA regulated in vitro diagnostic (IVD)1 device investigations. As described below, FDA does not intend to object to the use, without informed consent, of leftover human specimens -- remnants of specimens collected for routine clinical care or analysis that would otherwise have been discarded -- in investigations that meet the criteria for exemption from the Investigational Device Exemptions (IDE) regulation at 21 CFR 812.2(c)(3), as long as subject privacy is protected by using only specimens that are not individually identifiable. FDA also intends to include in this policy specimens obtained from specimen repositories2 and specimens that are leftover from specimens previously collected for other unrelated research, as long as these specimens are not individually identifiable. (*Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable*, <http://crpac.od.nih.gov/FinalFDAGuidanceonICforIVDDeviceStudieswithLeftoverSpecimensthatAreNotIndividuallyIdentifiable.pdf>)

Tool D

HIPAA Privacy Rule Issues for Repositories

The following article first appeared in the International Society for Biological and Environmental Repositories Newsletter, Volume 4, Issue No. 1, Fall 2004 (<http://www.isber.org/newsletters/Fall2004.pdf>)

I. Models for the Implementation of the HIPAA Privacy Rule for Repositories:

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule has created many challenges for human specimen repositories. Considerable confusion exists about how the Rule applies to such repositories, particularly with regard to when authorization is not required, whether informed consent for future unspecified research is still permitted, and how the Privacy Rule applies when a linking code to patient identities is retained. This article discusses some of these issues and proposes some possible models that may be considered for the implementation of HIPAA by repositories.

The Department of Health and Human Services (HHS) issued the HIPAA Privacy Rule on August 14, 2002³². This federal regulation, which went into effect for most institutions on April 12, 2003, governs the protection of individually identifiable health information with the intent of increasing the privacy of such information. The Privacy Rule covers individually identifiable health information that is held or maintained by “covered entities” (health plans, health care clearinghouses, or health care providers who transmit health information electronically for certain transactions as defined by HHS) or by business associates acting for a covered entity.

The Privacy Rule can have major implications for repositories and they need to consider how the regulation may apply. The Privacy Rule does not apply to human biological specimens per se, but it may apply to the identified information associated with those specimens. The first question to consider is whether the repository or its collecting sites are considered part of a Covered Entity. If so, the Privacy Rule may apply, depending upon the type of health information that may be collected, used or disclosed by the research repository or database. The Privacy Rule requires authorization from individuals before their protected health information can be used in research, unless an exception applies. This authorization is distinct from informed consent, which is a separate process.

Authorization for the use or disclosure of health information for research is not required if one of the following applies:

- Documentation has been obtained that an IRB or Privacy Board has waived the Authorization requirement in accordance with the conditions specified in section 164.512(i).
- The use or disclosure of protected health information (PHI) is used for reviews preparatory to research with representations that satisfy section 164.512(i)(1)(ii) of the Privacy Rule.

³² <http://www.hhs.gov/ocr/>

- The use or disclosure of PHI is for research on decedents' protected health information (PHI) with representations that satisfy section 164.512(i)(1)(iii) of the Privacy Rule.
- Only a limited data set is provided and there is a data use agreement with the recipient as specified under section 164.514(e).
- The use or disclosure of PHI is based on permission obtained prior to the compliance date of the Privacy Rule—informed consent of the individual to participate in the research; an IRB waiver of such informed consent; or Authorization or other express legal permission to use or disclose the information for the research as specified under section 164.532(c) of the Privacy Rule. (the “transition provisions”)
- The covered entity has de-identified the PHI according to standards set forth in the Privacy Rule so that its use and disclosure are not covered by the Privacy Rule.

A covered entity may also use or disclose PHI from databases and repositories for other purposes without Authorization as permitted by the Privacy Rule, such as if required by law or to a public health authority for a public health activity (e.g., disclosures to cancer registries).

A key factor in determining how the Privacy Rule applies to a collection is the types of data that are associated with the specimen. For example, the Privacy Rule does not apply if the repository or collecting site will not use or disclose any of the 18 identifiers that must be removed to create a de-identified dataset, and the Covered Entity has no knowledge that the information could be used to identify the patient. Patient authorization would not be required in such a case. Similarly, if the repository or collecting site is only using or disclosing a limited data set; i.e. a data set that does not contain any of the 16 identifiers that must be removed to create a limited data set, that data may be used and disclosed without authorization as long as there is a data use agreement with the recipient. A data use agreement is a written understanding between the covered entity and the recipient of the limited dataset that the recipient will not identify the subject that also meets the other requirements specified in the regulations. The use of a limited data set is often sufficient for repositories, because it can include complete dates and geographic identifiers, such as city, state and zip codes.

One of the challenges for repositories is determining how data can be used and disclosed if a specific research project has not been identified at the time the data are collected. The Privacy Rule does not permit authorization for future unspecified research and stipulates that authorization must be specific and meaningful. However, authorization may be obtained to create and maintain a research repository and no authorization would be required for subsequent use or disclosure of de-identified data or of a limited dataset with a data use agreement. Informed consent for unspecified research is still allowed, as clearly stated in the HHS educational brochure on Institutional Review Boards and the HIPAA Privacy Rule (<http://privacyruleandresearch.nih.gov/irbandprivacyrule.asp>). Informed consent and authorization are distinct concepts, which must be considered separately. Authorization is a

permission for use and disclosure of protected health information, whereas consent is a process that provides information about and agreement from the subject to participate in the research as a whole.

One common area of confusion is whether the Privacy Rule allows a code to be assigned that allows re-identification of the subject. As stated in the HHS educational document entitled *Institutional Review Boards and the HIPAA Privacy Rule* (<http://privacyruleandresearch.nih.gov/irbandprivacyrule.asp>):

“The Privacy Rule permits a covered entity to determine that health information is de-identified even if the health information has been assigned, and retains, a code or other means of record identification, provided that the code is not derived from or related to the information about the individual and could not be translated to identify the individual and the covered entity does not use or disclose the code for other purposes or disclose the mechanism for re-identification.”

It should be noted, however, that the HHS Protection of Human Subjects Regulations (45 CFR part 46) and the Privacy Rule have different definitions of identifiability and that the HHS regulations may apply even when the Privacy Rule does not and vice versa. These differences are explained in the HHS educational document entitled *Institutional Review Boards and the HIPAA Privacy Rule* (<http://privacyruleandresearch.nih.gov/irbandprivacyrule.asp>).

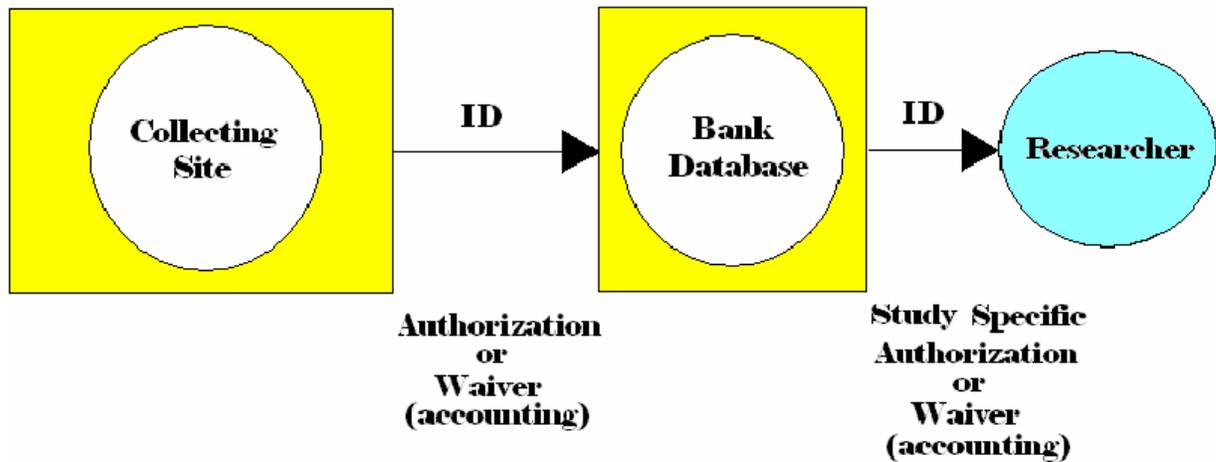
In determining how HIPAA applies to human specimen and/or data repositories, it is often useful to think about the repository in terms of two separate activities:

- a. the use or disclosure of data to create the research or repository database and
- b. the subsequent use or disclosure of data in the database for a particular research protocol.

This approach is particularly useful if, at the time the data are collected, the specific research use is not known.

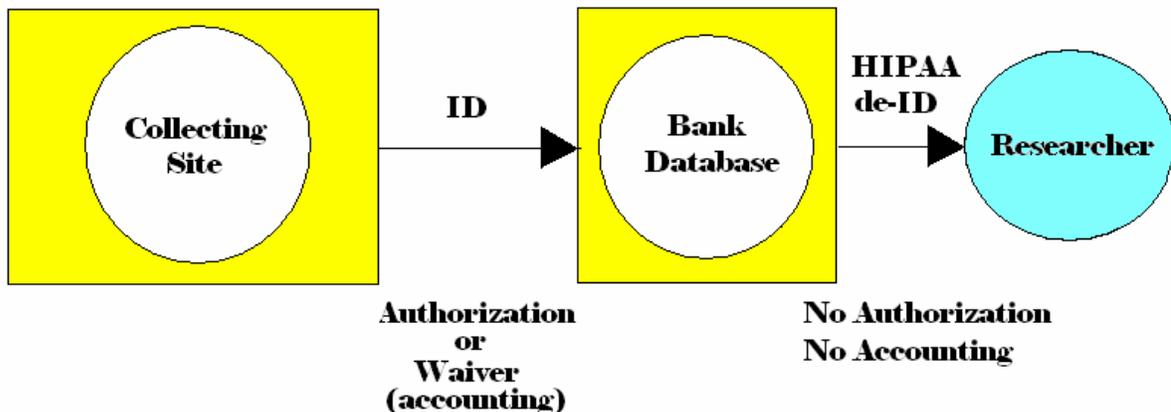
It may be helpful to use models, focused on the creation and subsequent research use of repository data as two separate activities, when considering how HIPAA applies to repositories. A few of these are shown in Figures 1 – 5. In these models both the collecting site and the research repository or database are considered part of a covered entity. The models address the requirements of HIPAA only; there may be additional requirements under the HHS (45 CFR part 46) or the FDA human subject regulations (21 CFR 50; 21 CFR 56) which are not addressed here.

Model 1



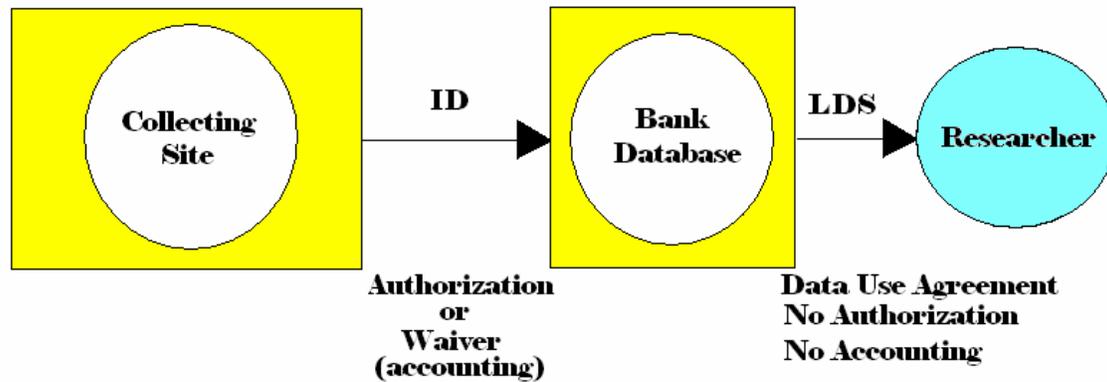
Model 1 illustrates a scenario where the data that are used to create the repository and the data disclosed to the researcher is considered identifiable under the Privacy Rule. That is, the dataset contains one or more of the 18 identifiers described in the Privacy Rule or is otherwise considered identifiable under the Rule. In this scenario, either an authorization or a waiver of authorization is required to create the database, (unless an exception applies, e.g. the conditions of the transition provisions have been met). A research-specific authorization or a waiver or alteration of the authorization would also be required if the information provided to the researcher is identifiable under the Rule. If waivers of authorization were obtained, such uses and disclosures would be subject to HIPAA's accounting provisions. (See attached definitions).

Model 2



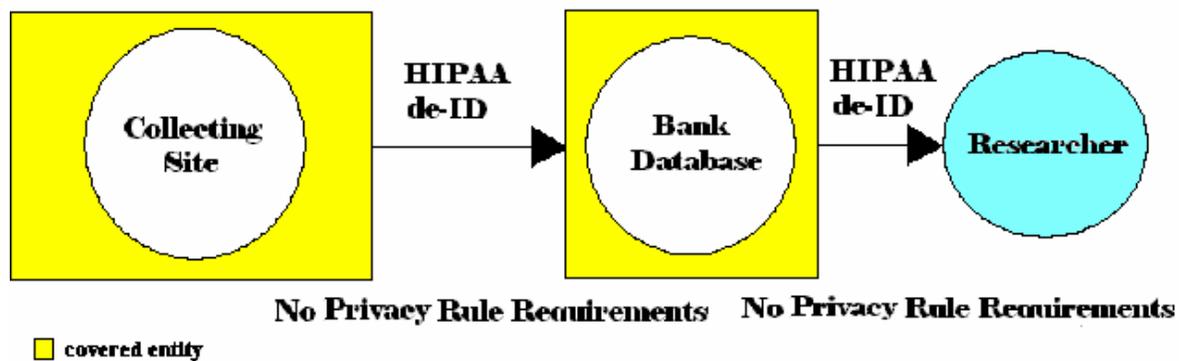
In Model 2, data that is identifiable because it contains one or more of the 18 identifiers under the Privacy Rule is used to create the database. However, only HIPAA de-identified data would be provided to the researcher. Authorization to create the database or a waiver of the authorization is required to create the database. However, research-specific authorization is not required for research use of the data because only HIPAA de-identified data is provided to the researcher. There are no accounting requirements.

Model 3



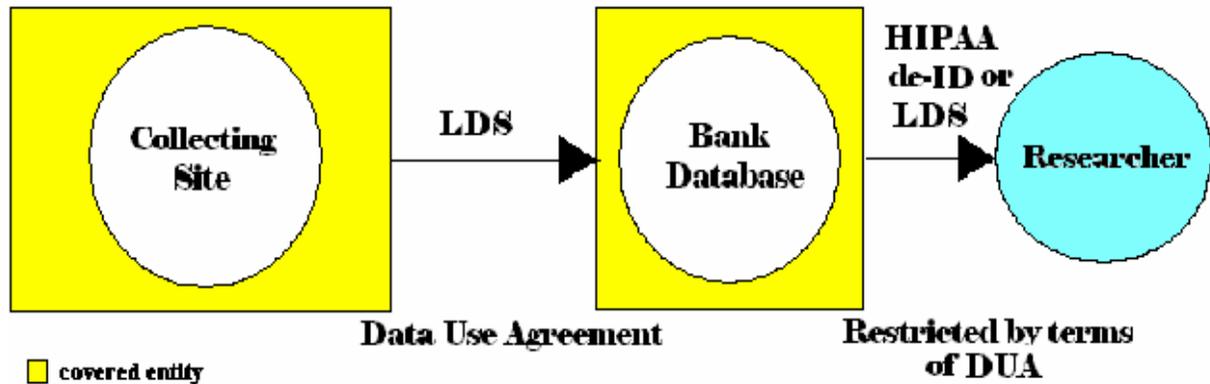
Model 3 illustrates a case where identifiable information is used to create the database or repository but only a limited data set (LDS) is provided to researchers. In this case authorization or waiver of authorization is required to create the database and a Data Use Agreement (DUA) would be needed between the covered entity releasing the data and the researcher receiving the data. There are no requirements for research-specific authorization or accounting of disclosures.

Model 4



Model 4 is a scenario where the database or repository only contains data that is de-identified under the Privacy Rule. There would be no Privacy Rule requirements either to create the repository or to use and disclose the data for research.

Model 5



In Model 5, a limited dataset (LDS) is used to create the database or repository. That is, the dataset that is being used to create the database does not contain any of the 16 identifiers that must be removed to create a limited dataset. A data use agreement (DUA) between the covered entity providing the limited data set and the bank receiving the limited dataset is required. HIPAA de-identified data or, a limited dataset could be provided to the researcher if there is a DUA with the researcher, provided that this does not violate the conditions of the initial Data Use Agreement between the collecting site and the bank database.

These are a few of the possible models that may be considered in creating and using repository data in compliance with HIPAA. Other models than those shown here may also be possible. The appropriateness of a model for a given situation depends upon many considerations, including the precise type of data being collected and disclosed by the repository, the relationship of the repository to the covered entity and other factors. Repository managers should always review the regulation and guidance material available on the HHS Office of Civil Rights (OCR) website and discuss these models with the appropriate institutional officials to determine the applicability of a specific model to a particular situation. Additional educational documents may be obtained from the NIH Privacy Rule and Research website (<http://privacyruleandresearch.nih.gov/>). Specific information pertaining to repositories is found in the educational brochures entitled, *Research Repositories, Databases and the Privacy Rule* (http://privacyruleandresearch.nih.gov/research_repositories.asp), and *Institutional Review Boards, and the HIPAA Privacy Rule* (<http://privacyruleandresearch.nih.gov/irbandprivacyrule.asp>). Repository managers should also consider the requirements of other applicable regulations, such as the HHS or FDA human subjects regulations and any relevant state and local laws, as these are not addressed here.

Definitions¹

Accounting of Disclosures - The Privacy Rule permits individuals to obtain a record of certain disclosures of their PHI by covered entities or their business associates, including disclosures made by researchers who must comply with the Rule. These accounting provisions do not apply to disclosures

Authorization – An individual’s written permission to allow a covered entity to use or disclose specified PHI for a particular purpose.

Covered Entity – A health plan, a health care clearinghouse, or a health care provider who transmits health information in electronic form in connection with a transaction for which HHS has adopted a standard.

Data Use Agreement (DUA) – An agreement into which the covered entity enters with the intended recipient of a limited data set that establishes the ways in which the information in the limited data set may be used and how it will be protected.

De-Identified Data Set (De-ID) – A dataset in which all 18 elements that could be used to identify the individual as stipulated in the Privacy Rule have been removed and the covered entity has no actual knowledge that the remaining information could be used alone or in combination with other information to identify the individual.

Identifiable Data Set (ID) - For the purposes of this document, an identifiable data set would be one that would be considered individually identifiable under the HIPAA Privacy Rule. For example, the dataset contains names, social security numbers, medical record numbers or one of the other 18 direct or indirect identifiers that must be removed for a de-identified dataset.

Limited Data Set (LDS) – Protected health information that excludes 16 categories of direct identifiers. A limited dataset may include complete dates and geographic information (excluding street address).

Protected Health Information (PHI) – PHI is individually identifiable health information transmitted by electronic media, maintained in electronic media, or transmitted or maintained in any other form.

II. Comparison of informed Consent and HIPAA Privacy Rule Authorization for Use of Human Specimens and Associated Data:

Determination of when consent and/or authorization are required depends on several critical factors. It should be noted that consent and authorization are not the same. Consent is a process mandated by the Common rule and the FDA human subjects regulations, which ensures that a research subject is fully informed about the benefits and risks of the research and that the process is documented by a signed document. Authorization as required by the HIPAA Privacy Rule is simply an agreement by a patient that 'protected health information' (e.g. identified health information maintained in a covered entity) may be used or disclosed.

Requirements for Informed Consent

Informed consent should describe the risks and benefits of the research and provide subjects enough information to allow them to make an informed choice about whether to participate. Ideally, the consent obtained at the time of obtaining tissue for placement into a bank should include a description of the type/s of research that the specimens will be used to support.

The FDA regulations and the Common Rule have the same requirements for the elements that must be included in an informed consent regardless of the type of research. These are listed below.

- Elements of a valid consent required by Common Rule and FDA regulations:
 - a) A statement that the study involves research
 - b) An explanation of the purposes of the research
 - c) The expected duration of the subject's participation
 - d) A description of the procedures to be followed
 - e) A description of any reasonably foreseeable risks or discomforts to the subject
 - f) A description of any benefits to the subject or to others which may reasonably be expected from the research
 - g) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained
 - h) For research involving more than minimal risk, an explanation as to whether any compensation, and an explanation as to whether any medical treatments are available, if injury occurs and, if so, what they consist of, or where further information may be obtained
 - i) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject
 - j) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits, to which the subject is otherwise entitled
 - k) Additional elements, as appropriate
 - l) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent
 - m) any additional costs to the subject that may result from participation in the research

- n) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject
- The following elements, while not required are desirable to include in an informed consent to collect specimens for a bank:
 - a) A description of how the specimens will be obtained;
 - b) How the specimens will be maintained in the bank (i.e., with or without identifiers);
 - c) Whether or not the specimens will be altered or simply stored 'as is;'
 - d) Who will be able to access the specimens and for what types of research
 - e) Whether or not identifiable information will ever be given to recipient investigators;
 - f) Information regarding how a subject can withdraw consent for use of his/her specimen in research.

Some general requirements related to consent for use of specimens and data include:

- Research on specimens or data should be consistent with the terms of the original informed consent. Specimens or data should not be used for research beyond the scope of the original consent without additional IRB review and approval.
- Under the Common Rule, informed consent or waiver of consent is required when identifiable specimens from living individuals are provided for research.
- FDA regulations require informed consent for the collection and use of specimens. There is no waiver except for emergency use. (Note, the initial consent for collection may allow use in subsequent research.). The FDA has, however, issued guidance concerning regulatory enforcement discretion of the informed consent requirement for use of specimens in invitro diagnostic studies if certain conditions have been met. (*"Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable"*).
- When coded specimens are accessed from a tissue bank that maintains identifiable specimens and the researcher cannot readily ascertain the subjects identity because of a written agreement or equivalent protection access subject identifying information, such research does not require specific consent or a waiver of consent if the conditions of the OHRP *"Guidance on Research Involving Coded Private Information or Biological Specimens"* (2004) applies.

Requirements for HIPAA Privacy Rule Authorization

Authorization only applies to the use and disclosure of protected health information as defined in the HIPAA Privacy Rule. This means that collection of specimens without any associated protected health information does not require authorization. Collection of subject data only requires authorization if it meets the definition of protected health information.

The HIPAA Privacy Rule defines the elements required for authorization as shown below:

- a) A description of the information to be used or disclosed that identifies the information in a specific and meaningful fashion
- b) The name or other specific identification of the person(s), or class of persons, authorized to make the requested use or disclosure

- c) The name or other specific identification of the person(s), or class of persons, to whom the covered entity may make the requested use or disclosure
- d) An expiration date or an expiration event that relates to the individual or the purpose of the use or disclosure
- e) A statement of the individual's right to revoke the authorization in writing and the exceptions to the right to revoke, together with a description of how the individual may revoke the authorization
- f) A statement that information used or disclosed pursuant to the authorization may be subject to redisclosure by the recipient and no longer be protected by this rule;
- g) Signature of the individual and date; and
- h) If the authorization is signed by a personal representative of the individual, a description of such representative's authority to act for the individual.

Some basic requirements related to authorization include:

- The Privacy Rule generally requires authorization or waiver of authorization whenever protected health information is used in or disclosed by a covered entity.
- However, data may be disclosed without authorization in some circumstances
 - as a de-identified dataset (see definitions in Tool D) or
 - as a limited dataset with a data use agreement (see definitions in Tool D)
- Data from decedents may be disclosed without authorization if the covered entity receives suitable documentation that the patient is deceased and some other requirements are met.
- Data collected under a valid permission, e.g. consent or waiver of consent prior to the implementation of the Privacy Rule (April 14, 2003), is grandfathered and requires no authorization if certain conditions are met.

A few of the basic rules for use of human specimens in research are highlighted below:

Specimens specifically obtained as part of a research project always require informed consent or waiver when there is direct interaction with the subject from whom the specimens or data are collected or if identified data are obtained.

Authorization or waiver of authorization is generally required for the collection and use of data within a covered entity when protected health information is obtained with the specimen.

The use of residual specimens and data, obtained for clinical care:

- Require no consent if the investigator cannot identify the subject from whom the specimens or data were collected.
- If HIPAA de-identified, require no authorization

Data that is not considered identifiable under the Common Rule (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information)

- may not be de-identified under the Privacy Rule since the presence of any of 18 Privacy Rule specified renders the data identified under the Privacy Rule.
- If the specimen or data is identifiable under the Common Rule:
 - Common Rule requires informed consent or waiver

- FDA regulations require informed consent for any research that will involve a submission to the FDA or is otherwise subject to the FDA regulations. (Note FDA allows waiver only for emergency use of a drug or device)

Requirements for use of specimens and data from deceased individuals:

Note that Common Rule does not consider deceased individuals to be human subjects and use of specimens and data from those individuals are not subject to the regulation. The FDA regulations do not address the issue of whether or not deceased individual are covered and the Privacy Rule requires that the covered entity be given sufficient information to determine that the patient is deceased before they release protected health information.

The requirements for consent and/or authorization arise again when specimens are transferred from a bank to a researcher. The heterogeneity of banking activities renders a one-size-fits-all answer impossible.

Tool E

Managing Risks in the Context of Research Using Human Specimens

Potential risks to subjects whose specimens and associated health data are used in research may include physical risks, particularly if the specimens are taken specifically for research purposes. Physical risks can include those involved with medical procedures, such as blood draws or extra biopsies taken for research purposes. Often, however, residual specimens taken during the course of routine medical care (e.g., diagnostic specimens) are used for research, which means that additional physical risk beyond that involved in the diagnostic procedure generally is not incurred. In some cases researchers might request permission from patients to take extra tissue for research during the course of clinical care, for example, an extra 5 cc of blood. In these situations, there is usually minimal additional physical risk.

The primary risk in research using human specimens is likely to be loss of privacy and confidentiality, which can occur anywhere along the continuum of obtaining, storing and distributing materials for research use. Concerns about breeches of confidentiality have increased as a result of advances in genetic and other molecular technologies, as well as the broad sharing of data made possible by sophisticated information technologies. Today, research involving specimens has the potential to identify genetic or other molecular alterations that may have implications for an individual's current or future health, or that of their immediate family, such as the presence of disease or other unsuspected risks. In addition, the improper use or disclosure of such information could result in psychosocial harms (such as anxiety) or the loss of employment or insurability.

An additional risk to subjects involves the improper use of unvalidated research results for clinical decision-making. This includes the use of the results of tests that have not been approved by FDA or performed in Clinical Laboratory Improvements Amendments (CLIA)-approved laboratories for patient treatment and care (discussed later in this paper).

In addition, in some cases, research on human specimens and associated health data also could raise risks to groups of individuals. For example, research using specimens may determine that a particular group of individuals (e.g., a specific racial or ethnic group) have an increased risk of developing disease. Disclosure of such information could have implications for insurability and/or employment and the potential for stigmatization. Fathoming the desires of the subject is often difficult when there is the potential for group harm from possible stigmatization of the group. IRBs must be sensitive to this concern when reviewing the requests for subsequent research activity and examine the sampling schemes both for the bank and for the tissues or data to be examined. Consultation with leaders in the groups likely to be affected may be helpful.

A risk that is less quantifiable to the subject is that associated with future, unspecified, research purposes, i.e., the uses are unspecified at the time of the initial specimen banking. These are the risks that often give IRBs and ethicists the most pause. Here, the subject does not have the opportunity to speak for himself or herself given a specific research protocol; the IRB has the responsibility to assess risks and make decisions that do not abrogate the rights and welfare of the individual. The IRB must try to understand the subjects' interests and decide under what circumstances consent can be waived and when a new consent might be warranted.

Most of the risks associated with future, unspecified, research are non-physical harms; such as loss of confidentiality. The risks associated with loss of confidentiality can be mitigated in a number of ways, including anonymization, good security and privacy practices, and certificates of confidentiality.

Meeting the promise of research using human specimens requires that custodians and users of that material ensure that the proper safeguards are in place to meet ethical, and legal/ regulatory requirements. As discussed previously, the primary risk to subjects from bank or research records that contain identifiable private health information is breach of confidentiality by personnel with access to the information or another breach in security of repository databases containing such information,.

Early Planning

Groups or individuals planning to establish a collection of specimens for use in research should consider a number of issues, including the purpose and nature of the bank and anticipated future uses, early in the planning stages. Careful planning will allow subject consent forms to be made as comprehensive as possible, minimizing the need to re-contact subjects for future research projects. Repository managers responsible for repositories involving the collection of specimens and data from multiple collection sites should obtain evidence of institutional compliance with applicable laws and regulations early in the planning effort. The OHRP requirement that institutions participating in research obtain a Federalwide Assurance mandates a process that can be time consuming, particularly when foreign sites are involved. Bank developers also should begin a dialogue with their IRB and institutional officials early in the protocol development process to ensure that they are aware of and comply with relevant institutional policies and procedures and to avoid unnecessary problems and delays in the approval process.

Repository Administration and Oversight

Appropriate governance of bank operations includes defined mechanisms to establish policies and procedures needed to ensure human specimens are appropriately used and that the rights and welfare of subjects are adequately protected. One useful approach is to use steering committees and/or advisory boards to establish operating policies and procedures for the bank.

Formalized procedures and policies for providing human specimens to researchers help ensure that human specimens are used appropriately and that subject privacy and confidentiality is maintained. The research use should be consistent with the provisions of the subject informed consent. Only specimens necessary to meet the research goals of the proposed study should be provided by repositories. Processes for review of researcher requests for specimens may be established as needed to ensure that specimens are provided only for studies consistent with the purpose of the bank and expected to contribute to scientific knowledge and the welfare of the public.

It is advisable for banks to initiate a formal agreement with investigators prior to providing specimens. Such agreements should include provisions for safe handling of the material, its disposition after the research is complete, who is responsible if harm results from the use of the

material and any other important issues that could lead to disputes. The agreement should also state that investigators will only use the specimens for the research proposed in their request, will assure appropriate biosafety procedures, will follow applicable federal, state, and local regulations for the protection of human subjects, will make no attempt to identify subjects and will not share the specimens data with third parties. Data use agreements, as described by the Privacy Rule, also may be required and may be part of the investigator agreement. Some banks require documentation of IRB review and approval from the investigator's IRB before specimens are distributed, even when the identities of subjects are not provided to the investigator.

Banks can reduce risks by implementing procedures to prevent disclosure of subject identity:

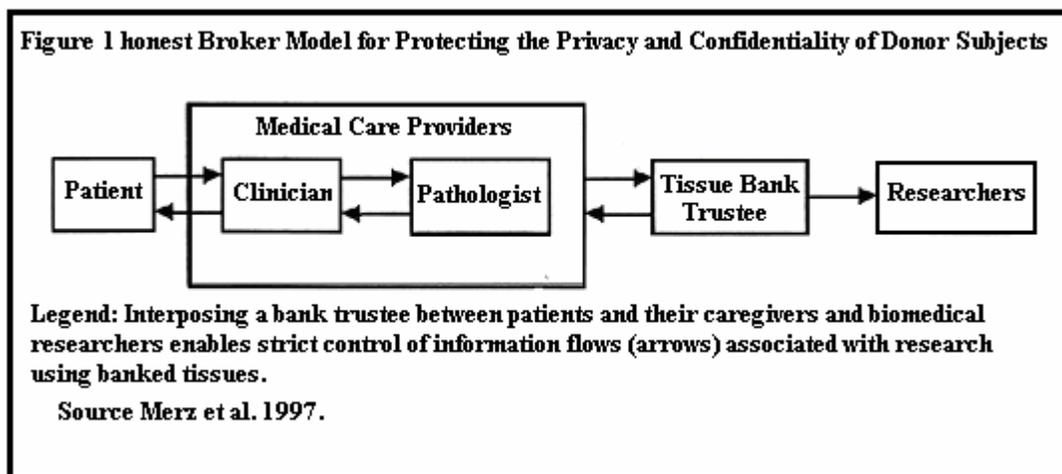
1. Have standard operating policies (SOPs) and training plans to ensure that information is appropriately protected and that information that could be used to identify the subjects is not disclosed to investigators.
2. Obtain written agreement from investigators not to attempt to re-identify subjects.
3. Require all bank personnel to sign confidentiality agreements stating that they will not disclose identifying information to third parties.
4. Ensure that HIPAA security regulations are implemented for the organization to provide secure protection of identifying information and the code/key to subject identities.

Privacy and Confidentiality of Human Subjects

A number of approaches are available to help minimize the probability of harms from breaches of privacy or confidentiality. While the safest route would be to absolutely block investigators from access to clinical information, it would also stop most important human specimen research. Some approaches that can be used to assure that subject privacy and confidentiality is protected include the use of honest brokers or firewalls to prevent access to identifying information, confidentiality agreements that bind employees to not reveal identifying information, clear written operating policies and high quality data security practices.

Banks should establish operating procedures and policies that minimize risks to subject privacy and confidentiality. In general, it is advisable to limit identifiers and/or identifiable private information retained by the bank to those that are required for the anticipated research use. Generally it is not necessary to include any direct identifiers on specimens and data provided to researchers. If future data (e.g. recurrence or outcome) is needed, coding can provide a link that will allow the resource to retrieve subject records at a later date. The honest broker model, where a trustee not participating in the research removes identifying information before the specimens are sent to the researcher, provides a way to secure links. The honest broker model is elaborated below.

Merz et al.³³ proposed the “honest broker” model illustrated in figure 1.



In this model, the bank functions as a “trustee” with the role of protecting subjects. The trustee serves as an intermediary between the human specimen sources and the researchers to control access to subject data associated with the human specimens and protect the privacy of subjects while facilitating research. The honest broker model allows a one-way flow of information from the bank trustee to the researcher. The trustee de-identifies the research specimens and data by removing subject identifiers, replacing them with a linking code to allow the trustee to re-identify specimens and data. This approach prevents the researcher from knowing identities of subjects, while permitting access to follow-up data as needed. While a number of organizations use the honest broker model, the stringency of the various approaches varies. The critical factor for any system to work is that the honest broker be independent and able to function without interference or pressure to breach subject privacy or confidentiality. While honest broker systems have many benefits, they require significant investment and infrastructure support from the sponsoring institution.

³³ Mertz JF, Sankar P, Taube SE and LiVolsi V. Use of Human Tissue in Research: Clarifying Clinician and Researcher Roles and Information Flow. *J Investig Med* 45:252-257. 1997.

The critical characteristics of an honest broker include:

1. No involvement in the research or vested interest in the research results)
2. Independence and authority supported by the institution/
3. Operate under written, well defined operating procedures and policies covering who has access to specimens and the codes/key to subject identities
4. Be required to report/document any episodes of disclosure of key/code or pressure to disclose subject identities

As further protection, unique codes unrelated to subject identities should be used whenever possible (e.g. names or initials should not be included on specimen containers or released from the repository with associated specimens and/or documents). Storage of direct identifiers such as name and Social Security number may be critical in some situations (long-term follow-up studies). When direct identifiers are retained they should be securely stored and be accessible only by a few authorized individuals. Technologies such as encryption have been used successfully to protect subject identity.

Employee confidentiality agreements can also help protect patient privacy and confidentiality. These agreements bind bank employees to neither reveal confidential information, such as patient names or other identifying information, nor to use confidential data for anything but authorized banking activities. Employees should be made aware that any disclosure or other misuse of subject information is strictly prohibited and the consequences for violating the agreement.

Bank managers and/or researchers using human specimens should also consider using Certificates of Confidentiality, issued by the National Institutes of Health, to further protect subject confidentiality (<http://grants.nih.gov/grants/policy/coc/index.htm>). Certificates of Confidentiality allow researchers to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. Certificates of Confidentiality may be granted for studies collecting information that if disclosed could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation, and these certificates cover specimen and data repositories. Certificates of Confidentiality may not be appropriate for all types of repositories. The NIH Certificates of Confidentiality Kiosk (<http://grants.nih.gov/grant/policy/coc/index.htm>) should be consulted for additional information.

Tool F Patient Attitudes

Several U.S.-based studies have examined attitudes regarding informed consent for the collection and/or use of their human biological materials (see table). These data suggest that the public maintains a strong interest to having their samples used in research. Between 53-90% of individuals in these studies were willing to provide consent for research to be conducted with their samples if asked. This willingness generally includes unspecified future research. Chen et al. 2005 reported that only 1.2% of research participants would limit future research to their own medical condition and not allow research on other medical conditions. There is also considerable anecdotal evidence that indicates that most patients who are approached about allowing their specimens and data to be banked for future research agree to allow unspecified future uses.

The study data also suggest that most respondents want to know that their samples and data are being used for research before their samples are used. One study found this preference to be stronger in reference to research with clinically-derived samples as compared to research derived-samples (Wendler and Emanuel 2002), and another study established that a majority of individuals wanted the opportunity to provide consent even when samples would be anonymous. (Schwartz, Rothenberg et al. 2001). Wendler and Emanuel, 2002 suggest that once consent for research use is obtained, many subjects may find notification of additional research use with the opportunity to 'opt out' is sufficient. In Europe, some countries have used an 'opt out' approach in which patients are informed that samples may be used for research and given the opportunity to indicate that they do not want their samples used.

The following table provides references on patient attitudes and summarizes the results for each paper.

<i>Citation</i>	<i>Population</i>	<i>Research Question</i>	<i>Research Findings</i>
Wang, Fridlinger, Sheedy, Khoury (2001) "Public Attitudes Regarding the Donation and Storage of Blood Specimens for Genetic Research" Community Genetics, 4(1): 18-26.	-American Healthstyles Survey used. Four questions posed re: blood donation/storage for genetic research in 1998 survey. -2,621 of 3,130 participants (84%) completed these questions.	-Public attitudes towards blood donation and storage of genetic samples and characteristics of participants that correlate with favorable positions on donation/storage issues.	-43% favored donation and storage. 36% favored donation or storage. 21% were not willing to donate or store samples. -Favoring donation and storage correlated with: 1) belief that genetic research will prevent disease (odds ratio [OR] 2.9; p<0.001); 2) belief in genetic determinism (OR 1.5; p<0.004); 3) agreement to participate in government research (OR 2.9; p<0.001). -Demographic characteristics indirectly associated with attitudes toward donation/storage: 1) higher education; 2) white race; 3) living in Mountain/Pacific or mid-Atlantic regions of U.S.; 4) positive family history of genetic disorder (p<0.05).
Willison et al (2003) "Patient Consent Preferences for Research Uses of Information in	-Semistructured interviews conducted with 17 patients. -Structured fixed response survey	-Patient preferences for method of consent for use of information from	-Majority of patients (74%) preferred that active consent be sought before information is used for research. -Little or no distinction by patients between identifiable and anonymised data.

Electronic Medical Records: Interview and Survey Data," BMJ, 326: 373.	conducted with 106 patients. -Conducted in family practices in southern Ontario, Canada.	electronic medical records for research.	-Research sponsored by drug and insurance companies caused most concern in interview group. 51% of survey respondents had moderate to high concerns over research funded by insurance companies and 43% had similar concerns over government sponsored research; difference in concern was not significant. Funding by foundations and drug companies caused less concern, with differences in response not significant.
McQuillan et al (2003) "Consent for genetic research in a general population: the NHANES experience," Genetics in Medicine, 5(1): 35-42.	-Data from 1999 and 2000 NHANES, a nationally representative survey of U.S. household population aged 20 years or older.	-Sociodemographic factors associated with consent for storage of DNA for future genetic research.	-84% and 85.3% of eligible participants consented to inclusion of blood samples in national repository for genetic research in 1999 and 2000, respectively. -Females and blacks were least likely to consent (1999, 82.2% and 73.2%; 2000, 83.6% and 81.3%, respectively). Non-Hispanic black race/ethnicity significantly predicted for not consenting to future genetic research.
Stegmayr and Asplund (2002) "Informed consent for genetic research on blood stored for more than a decade: a population based study" BMJ, 325:634-5.	-Follow up on 1409 of the subjects randomly selected men and women, aged 25-64 years, who participated in the 1990 risk factor survey in the World Health Organization's MONICA project.	-Proportion of subjects who would consent to academic and industrial genetic research with their own samples, previously collected for non-genetic research.	-1311 out of 1409 subjects (93.0%) consented to academic genetic research. -Of 1311 subjects, 292 (22.3%) requested contact and new consent for each new research project. -A comparable proportion gave consent to industrial research.
Womack and Jack (2003) "Family attitudes to research using samples taken at coroner's postmortem examinations: review of records" BMJ, 327:781-2.	-English coroner's officers identified deaths that required postmortem examination. Families of the deceased were contacted by phone by research nurse at Peterborough District Hospital for telephone interview.	-Effect of adverse publicity re: hospitals retaining tissues and organs at post mortem without consent on family responses to requests for such samples.	-75 of 106 families (71%) agreed to interview. -Reasons for refusal of interview almost never involved negative publicity. -All who agree to interview gave consent for samples to be taken.
Schwartz et al (2001) "Consent to the Use of Stored DNA for Genetics Research: A survey of Attitudes in the Jewish Population," American Journal of Medical Genetics, 98: 336-342.	-Jewish men and women, aged 18-90 years, in the Baltimore-Washington, DC Metropolitan area. Final sample consisted of 273 Jewish individuals who completed the telephone interview.	-Relationship between willingness to participate in genetic research and 1) setting in which material is collected and 2) characteristics of disease/trait under study.	-Majority (60-75%) believe consent is necessary for collection of samples in both clinical and research settings. Participants were more likely to believe in need for consent in clinical rather than research settings. -Individuals were less likely to participate in genetic studies examining potentially stigmatizing or stereotypical traits. -Younger age (e.g. those under 50), higher educational level (e.g. college/post-graduate), and belief that community consent is necessary predicted for greater insistence on need for informed consent across all scenarios. -Stronger identification with Jewish cultural

			identity predicted greater willingness to participate in genetic studies across scenarios and illnesses/traits.
Wendler D, Emanuel E. (2002) "The debate over research on stored biological samples: what do sources think?" Arch Intern Med. Jul 8;162(13):1457-62.	-Telephone survey of 504 individuals. Two cohorts studied: 1) individuals who had previously participated in clinical research and contributed samples and 2) randomly selected Medicare patients.	-Individuals' attitudes regarding when their consent should be obtained for research on stored biological samples.	-65.8% of respondents would require consent for research on clinical derived, identifiable samples; 27.3% would require consent for on clinically derived, "anonymized" samples. -29.0% of respondents would require consent for use of research derived, identifiable samples; 12.1% would require consent for use of research derived, "anonymized" samples. -88.8% of respondents would want to be informed of results that have uncertain clinical significance. -91.9% of respondents would not impose greater safeguards on future research on a different disease than the one originally studied at the time of sample procurement.
Malone T, Catalano PJ, O'Dwyer PJ, Giantonio B. (2002) "High rate of consent to bank biologic samples for future research: the Eastern Cooperative Oncology Group experience." J Natl Cancer Inst. May 15;94(10):769-71.	-Between February 1998 and October 2000, 5411 patients in 40 Eastern Cooperative Oncology Group (ECOG) coordinated trials were given an original consent paragraph on tissue banking. 2154 patients in seven trials were given a newer (ISBC-revised) consent form, featuring three separate consent questions.	-The relationship between increases in patient protection (i.e. level of detail in informed consent forms) and assent rates for future storage and use of samples.	-consent rates were high in all cases. 89.4% of patients signed the original ECOG form, 93.7% signed question 1 of the ISBC-revised consent form, 86.9% signed question 2, and 84.3% signed question 3. -Increased patient protection and substantial availability of biologic samples are not mutually exclusive.
Jack AL, Womack C. (2003) "Why surgical patients do not donate tissue for commercial research: review of records." BMJ. Aug 2;327(7409):262.	-Interviews by research nurses with patients at Peterborough Hospitals NHS Trust tissue bank in England. -Records of consecutive nurse-patient interviews between October 1, 1998 and August 31, 2002 were also reviewed.	-Whether or not commercial use of tissue might deter some patients from donating.	-Generally, donation of surgically removed tissue to biomedical research in the commercial sector is unproblematic for most patients. -Patients distinguish between research using tissue from living versus dead people.
Kass NE, Natowicz MR, Hull SC, Faden RR, Plantinga L, Gostin LO, Slutsman J. (2003) "The use of medical records in research:	-602 participants were interviewed from March 1996 until February 2000. -Participants had a serious genetic or other chronic medical	-Conditions under which use of medical records for research purposes is deemed acceptable by research	-Only 31.1% of patients agree that researchers should have access to medical records without getting permission first. -When assured that privacy and confidentiality would be protected, a majority of participants (71.4%) agreed to the formation of a secure health database for researchers and a majority approved

<p>what do patients want?" J Law Med Ethics. Fall;31(3):429-33.</p>	<p>condition or a family history of such a disorder. -Participants recruited from outpatient clinics of Johns Hopkins Hospital, Johns Hopkins ongoing research studies, disease registries within state of Maryland, and newspaper advertisements.</p>	<p>participants and whether disease or demographic group characteristics influence determinations of acceptability.</p>	<p>of an anonymous health database (85.9%). -In some cases, blanket consent may represent an acceptable compromise between no consent and full positive consent.</p>
<p>Partridge AH, Burstein HJ, Gelman RS, Marcom PK, Winer EP. (2003) "Do patients participating in clinical trials want to know study results?" J Natl Cancer Inst. Mar 19;95(6):491-2.</p>	<p>-51 patients from fifteen sites enrolled in a multicenter phase II study for first-line treatment of advanced breast cancer completed a questionnaire. -Median age was 54 years and 84% were white. 61% had college educations.</p>	<p>-Whether patients enrolled in clinical trials want to be informed about study results or not.</p>	<p>-Majority of patients (96%) wanted to be informed of results of trial. -Many women felt that their doctor should be responsible for sharing clinical trial results with them.</p>
<p>Merz and Sankar, "DNA Banking: An Empirical Study of a Proposed Consent Form" In R.F. Weir (ed), Stored Tissue Samples: Ethical, Legal, and Public Policy Implications. Univ. Iowa Press, 1998.</p>	<p>-Subject pool of 99 prospective jurors who were approached with a consent form and associated questionnaire that measured comprehension, attitudes, etc.</p>	<p>-Opinions and preferences of laypersons regarding stated willingness to give samples to genetic research studies.</p>	<p>-Subjects who have completed fewer years of education tend to have greater difficulty understanding informed consent forms. -Subjects' assessments of risks and benefits of genetic research do not correlate with stated willingness to donate samples. -Anonymity of samples is important to subjects; only half as many subjects would donate in a "linked" scenario as opposed to an "anonymized" scenario. -79% of respondents desire return of research results. Enacting this policy may prove problematic though. -Commercial uses of genetic material in research do not discourage subjects from giving samples.</p>
<p>"Lay Reactions to Pharmacogenetics Research: A Focus Group Study" NIGMS, December 1999, prepared by Lynne Donner under NIGMS contract #26-MD-914077.</p>	<p>-Focus group discussions with 30-60 year olds with at least a high school education, not employed in health care related work (or close to anyone in such work), and self-identified member of their racial/ethnic group.</p>	<p>-Objectives were to gain insight into consumers' perceptions regarding genetic research including: general thoughts, fears, misperceptions, assessments of benefits, willingness to enroll in studies, and comprehension</p>	<p>-In all ethnic groups, half or more participants in the discussion expressed willingness to participate in pharmacogenetics research involving donating a tissue sample via a mouth swab. -Willingness to participate was conditional and based on various factors: 1) what participation involves (e.g. decline taking experimental medications); 2) study goals; 3) study sponsor; 4) confidentiality; 5) effects on insurability; 6) time commitments; 7) potential benefits to family; 8) availability of prior research or progress reports; 9) whether or not personal/individual information is returned to subjects.</p>

		of a pharmacogenetics fact sheet.	
Taylor, H. "Majority Supports Idea of DNA Databank and Favors Government Commission to Address Use and Abuse of Genetic Testing", The Harris Poll 1995 #34	-Telephone poll in United States between April 6 and 9, 1995. Nationwide cross section of 1000 adults, representative of actual demographic proportions in US population.	-Assessing attitudes of members of U.S. population towards creation of a DNA Databank.	-60% of those polled are very concerned that insurers or employers may use genetic test results in a discriminatory fashion. Another 26% are somewhat concerned. -When asked about the acceptability of a DNA Databank that collects DNA from each newborn child and links the information with the child's identity, 28% found this very acceptable, 28% found it somewhat acceptable, 16% found it not very acceptable, 27% found it not at all acceptable, and 1% were not sure. -48% of those polled found it very important to have a government commission recommend policies to protect the privacy of genetic tests. Another 37% considered it somewhat important.

Tool G

Reporting Research Results to Subjects

Recent surveys show that research subjects often expect, if not demand, to receive research results, although many of these surveys include individuals participating in ongoing clinical trials, not donating human specimens for research.³⁴ There is ongoing debate about whether individual research results should be communicated to subjects, either upon completion of a study or at some later date in time. This issue is relevant to all human subject research, not just research involving human specimens. However, research involving human specimens can be conducted years, if not decades, after the material was first collected, thereby raising some additional questions about investigators' responsibilities to report potentially useful information to subjects. Clearly, many of these issues are not relevant if the subject identities are not known by the researcher, which is the case for much human specimen research.

The argument for reporting the research results is primarily based on an assumption that subjects have a right to know any results that might be useful to them or their care providers. Those who believe that subjects have the right to research results believe that the principle of autonomy gives subjects the right to know what has been learned about them.³⁵

The argument for not reporting specific research results is they are often unvalidated or of uncertain clinical significance. Use of unvalidated results, particularly for clinical decision making, may pose risks to the subject. The harms include extreme distress, unnecessary and sometimes harmful medical interventions and even death. Subjects and/or their medical care providers have made irreversible decisions based on information that ultimately has proven false. As an example, some women without breast or ovarian cancer decided to have prophylactic radical mastectomies after receiving positive results in experimental genetic tests for BRCA1 and/or 2. Once better prevalence data were gathered, these tests were shown not to be definitive indicators of disease. In another case, a group of breast cancer researchers using an unvalidated test to diagnose recurrence in their patients returned individual results that led to mental disorders and in at least one case, death by suicide in a woman whose cancer had not returned.

Confusion about the appropriateness of returning individual research results has increased as a result of HIPAA's Standards for Privacy of Individually Identifiable Health Information (the Privacy Rule). The Privacy Rule provides individuals access to their medical records and other types of health information to the extent that the information is maintained within a "designated record set." and used to make decisions about the patient. Research information could be considered part of a designated record set if it is used in clinical decision making or for other reasons entered into the patient chart.

The Clinical Laboratory Improvement Amendments of 1988 (CLIA) must be considered in the decision to report research results to subjects. CLIA was passed in 1988 to establish quality standards for all laboratory testing and to ensure the accuracy, reliability and timeliness of patient test results regardless of where the test was performed. Under CLIA, a laboratory is

³⁴ Partridge Ann H, Burstein Harold J, Gelman Rebecca S, Marcom P. Kelly , and Winer Eric P. Do Patients Participating in Clinical Trials Want to Know Study Results? JNCI 95:491-2, 2003.

³⁵ Veatch, Robert M. A Theory of Medical Ethics. Basic Books Inc., 50 1981.

defined as any facility which performs laboratory testing on specimens derived from humans for the purpose of providing information for the diagnosis, prevention, treatment of disease, or impairment of, or assessment of health. CLIA regulations require that all reference laboratories be certified if they provide patient information for clinical care. CLIA certified laboratories may only disclose test results or reports to “authorized persons” as defined by state law. Most states do not consider patients/research subjects “authorized individuals.” However, some states allow patients to receive results under some circumstances. Tests conducted in non-CLIA laboratories cannot be used for clinical decision making. This argues that no benefit would accrue to the patient from receiving research results from a non-CLIA laboratory. However, if the results seem pertinent to the health or welfare of the subject and there is an approved test, they could be informed that testing in a CLIA laboratory might be beneficial.

The easiest way to avoid harms from unvalidated research results is to only provide reliable information. MacKay, 1984³⁶; Fost and Farrell³⁷, 1989 stated that subjects should not be provided individual research results until the findings have been confirmed through the development of a reliable, accurate and valid confirmatory test. However, it is appropriate and meets the requirements of autonomy to inform subjects by providing aggregate research findings through letters, newsletters or websites.

Anytime research results are returned to subjects the process should be reviewed by the IRB and a re-contact plan developed. Reilly has suggested that IRBs should develop general policies governing the disclosure of information to subjects to help make these determinations.³⁸ He advocates that at the very least, the following factors should be considered:

1. the magnitude of the threat posed to the subject;
2. the accuracy with which the data predict that the threat will be realized; and
3. the possibility that action can be taken to avoid or ameliorate the potential injury.

In 1999, NBAC also recommended that IRBs develop general guidelines for the disclosure of the results of research to subjects and require investigators to address these issues explicitly in their research plans, including a strategy for providing appropriate medical advice or referral. They noted that disclosure of research results to subjects represents an exceptional circumstance. Disclosure of research results should occur only when all of the following apply:

1. the findings are scientifically valid and confirmed,
2. the findings have significant implications for the subject’s health concerns, and
3. a course of action to ameliorate or treat these concerns is readily available.

Overall, there should be a compelling rationale for reporting research findings to subjects and if it is anticipated that such a need might arise, a plan for doing so should be included as part of the

³⁶ [MacKay CR](#). Ethical issues in research design and conduct: developing a test to detect carriers of Huntington's disease. [IRB](#). 1984 Jul-Aug;6(4):1-5.

³⁷ [Fost N, Farrell PM](#). A prospective randomized trial of early diagnosis and treatment of cystic fibrosis: a unique ethical dilemma. *Clin Res*. 1989 Sep;37(3):495-500.

³⁸ Reilly, Philip. "When Should an Investigator Share Raw Data with the Subjects?" *IRB* 2 (No. 9, November 1980): 4-5, 12.

protocol reviewed by the IRB. Subjects should be clearly informed in the initial consent process whether or not they will receive individual results from the project.

Tool H

Ownership of Specimens, Commercialization and Intellectual Property

The question of who owns a tissue once it is removed from the body is unresolved. The office of Technology Assessment published a report¹ in 1987 that reviewed what was known about ownership of human tissues and cells. The report concluded that:

No area of law clearly provide ownership rights with respect to human tissue and cells. Nor does any law prohibit the use or sale of human bodily substances by the living person who generates them or the one who acquires them from such a person, except under certain circumstances unrelated to biotechnology research.

Now, nearly 20 years later, the situation remains essentially unchanged. At the time of the OTA report there was only one case in U.S. law that addressed the questions of ownership and intellectual property related to use of human specimens. Today three have been resolved and two are pending. The bottom line remains the same, the courts have ruled that individuals have no right to ownership of their tissues once they are removed from the body and no inherent right to share in any profit made as a result of research using those specimens. These findings are consistent with centuries of common law related to ownership or control of cadavers and the common practice of pathology labs to hold and control use of clinical specimens as their guardian or trustee. A large body of existing law may apply to IP rights related to use of human tissues in research, including Patent Law, Autopsy and Cadaver Law, Blood and Semen Law, Copyright Law, Trade Secret law, Conversion & Trespass Law and Accession Law. Some of these laws played critical roles in the court cases discussed below. A good discussion of the issues surrounding ownership of human specimens and IP rights can be found in the article by Hakimian and Korn.² A recent review of state laws with respect to use of human specimens in research by Hakimian et al. found that no state laws specifically assign ownership rights.³

The three court cases in the United States that have been resolved are Moore V Regents of the University of California, Greenberg et al v Miami Children's Hospital and Catalona v Washington University. The Moore case involved charges by a patient with hairy cell leukemia that his physician had benefited from using spleen samples taken with a standard surgical consent form, but no research consent to develop a monoclonal antibody that had significant commercial value. Moore later signed a research consent allowing blood samples to be taken. He later consented to the research, but did not agree to waive his right to any commercial products that might be developed as a result of the research. Moore's claim was that his blood cells were appropriated without his consent and that he had the right to share any profit derived from the use of his biological specimens. This case went to the California Supreme Court, which ruled on it in 1990 that individuals do not retain any right of ownership when their tissue is used in the development of new products and no right to share the proceeds from IP that resulted from such use. Part of the reasoning in this ruling is that the product is the result of intellectual input from the inventor and not an inherent part of the tissue used in its creation. This is justified by the ability of the inventor to patent biological products. The court found that the operative law for such uses of tissue was not property law, but rather public policy and public health law. While the Moore case sets precedent only in California, it has been widely cited and was an important element in the Greenburg decision that will be discussed next

The Greenburg case, widely known as the Canavan's case, a group of families of children with Canavan Disease formed an organization, the Canavan Foundation, to encourage research on this rare genetic disease. They created a human specimen bank to make samples from Canavan patients available for research and recruited a group at the University of Miami to look at the genetics of the disease using their specimens. The result of that research was the discovery of the genetic defect responsible for the disease and the development of a test to identify carriers of the defective gene. When the University licensed the test and the parents discovered that the cost of the test was high enough that it could discourage testing for the disease, they sued in federal court. In May 2003 a Florida judge, in a ruling similar to that of the Moore case, that individuals do not retain rights to own or control specimens contributed for research. Unlike the Moore case, the judge found no requirement that the researchers disclose that there would be potential for economic gain from the research. Importantly the judge also found that granting a right for specimen provider to control the uses of the research results would have a chilling effect on research. The judge also found no rationale for specimen source to have any IP rights from the invention.

The Catalona case was resolved in United States District Court, Eastern District of Missouri, Eastern Division in March of 2006. The University and a researcher both claimed the right to a large specimen collection. William Catalona is a highly respected surgeon and researcher who studies prostate cancer. While working at Washington University in St. Louis, he developed a large collection of human prostate samples for use in his research. When he decided to take a position at another university, he assumed that he would be allowed to take his specimen bank with him. The university objected, claiming that they owned the collection because it had been assembled while Dr. Catalona was on the faculty and largely created using federal grant funding. Dr. Catalona's response was to ask his research subjects to withdraw their consent and to sign a new consent, which he presumed would transfer ownership to him. Washington University filed suit in federal court seeking to block the move of the bank to the new institution and claiming ownership of the samples. The court found that Dr. Catalona and eight research participants failed to demonstrate that they were entitled to any injunctive relief. It ruled that Washington University owns all the biological materials, that neither Dr. Catalona nor any research participant has any ownership or proprietary interest in the banked specimens. Finally, the court ruled that the new consent forms are void and ineffective to transfer ownership or possession of the stored specimens. The resolution of this case adds support to the previous decisions on ownership and intellectual property. One thing that makes this case different from some of the others is the issue of grant support for the creation of the collection. Under federal regulations, grants are awarded to institutions, not individuals, thus significantly strengthening the University's case for ownership.

Thus, in all three instances when the courts were asked to adjudicate, they found no basis to establish individual ownership of or right to control the use of excised tissue collected or used to develop research products, even while affirming the applicable principles of informed consent. None of the cases are binding in states other than in the jurisdictions where they were decided, but taken together create a compelling argument for the principles that all three courts upheld. Both the Moore case and the Greenberg case noted plaintiff's rights were violated by failure to secure prior consent for product development.

Two cases now pending may eventually have an impact on the questions of ownership and IP rights related to use of human specimens in research. While neither of these cases has been resolved, they raise some of the same issues raised in Moore, Greenburg and Catalona as well as some additional issues.

In the two pending cases the Havasupai Tribe of Arizona is suing former Arizona State University professor Therese Markow and her collaborators and Arizona State University and its regents in U.S. District Court in Phoenix. Two separate lawsuits initially filed in federal court, alleged that Markow used blood samples collected for a diabetes study for unrelated research that would not have been agreed to by the tribe or the individual participants in the research. One suit was filed by a group of tribal members and the other by the tribe. U.S. District Judge Frederick Martone ruled in April 2005 that a number of the allegations made by the individual tribal members in their lawsuit are without merit. Since these were the claims that supported filing in federal court, the ruling allowed the case to be moved to State Court. Again, the issues primarily relate to ownership and the right to use research specimens for purposes different from the research agreed to in the initial consent. Since these cases are now in state court, they won't be binding on other states and their outcome may have limited impact on the overall question of ownership.

In summary, the question of ownership and rights to intellectual property resulting from the use of human specimens remains unresolved. Given the tremendous increase in research using specimens and data and the potential for application of that research to the development of technologies and products of tremendous value, it would seem that these issues will be important for the foreseeable future.

References:

1. U. S. Congress, Office of Technology Assessment. New Developments in Biotechnology: Ownership of Human Tissues and Cells - Special Report. PTA-BA-337 (Washington DC: U.S. Government Printing Office, March 1987).
2. Hakimian R and Korn D. Ownership and Use of Tissue Specimens for Research JAMA, November 24, 2004, 292, 2500-2505.
3. Hakimian R, Taube S, Bledsoe M, Aamodt R. 50-State Survey of Laws Regulating the Collection, Storage, and Use of Human Tissue Specimens and Associated Data for Research. Rockville, MD: National Cancer Institute. 2004.

TOOL I STATE LAWS

Researchers need to be aware of state laws that confer additional protections for human subjects, and need to comply with these laws in addition to complying with federal regulations. Federal policy for protection of human research subjects (the Common Rule) “does not affect any State or local laws or regulations which may otherwise be applicable and which provide additional protections for human subjects.” 45 CFR 46.101 (f)

Most states have passed laws that limit the disclosure and use of medical information.³⁹ Since much research using human biological material requires associated patient information, researchers, repository managers, and IRBs should be aware of any state law requirements for the use of specimens and accompanying patient information. Some states permit disclosures of medical information for research purposes under certain conditions without the informed consent of individuals. Examples of some of these provisions permitting releases of information include allowing disclosures for research when the subject identities are not disclosed, when the data are “anonymous”, when an IRB approves, or when research is conducted pursuant to federal regulations (the Common Rule or FDA regulations for human subject protection).

More than half of the states restrict the use of genetic information or information derived from genetic tests. These statutes usually limit the use of information derived from clinical or diagnostic genetic tests and are intended to prohibit discrimination in the provision of insurance or employment. Certain state statutes specifically address the use of “genetic information” for research purposes. Often, these statutes permit the use of genetic information for research purposes when the identity of the individual is not disclosed, or under similar conditions to the state statutes allowing releases of medical information for research (see above).

Several states have enacted state statutes that extend the scope of the Common Rule to all research regardless of the funding source. Virginia, Maryland and New York require IRB review of all human subjects’ research, and prior informed consent of subjects. California has passed a law that requires researchers to obtain the informed consent of subjects or their legally authorized representatives prior to conducting human subjects research. Illinois and New Jersey has passed patients rights bills that require hospital patients to be informed if they are to be enrolled as research subjects.

The following table tabulates the state laws that may be applicable to use of human specimens. The presence of an * indicates that there is a provision related to the topic. It should be noted that there is considerable variation among states in the specific requirements of those provisions. In some cases there may even be inconsistent definitions or requirements in different statutes within a state.

³⁹ Hakimian R, Taube S, Bledsoe M and Aamodt R. 50-State Survey of Laws Regulating the Collection, Storage, and Use of Human Tissue Specimens and Associated Data for Research. U.S. Department of Health and Human Services, National Institutes of Health. NIH Publication No. 05-5628. November 2004.

In the table that follows, an asterisk (*) indicates areas that are covered in the laws and regulations of the listed state.

STATE	Disclosures of Medical Information Permitted for Research		State Laws for Human subjects Protection	Conditions Imposed on Genetic Testing/ Genetic Information	Genetic Information Defined as Personal Property
	For Anonymous Data (or Identity Protected)	With IRB Approval or When Federal Rules Apply			
ALABAMA				*	
ALASKA	*	*		*	
ARIZONA	*	*		*	
ARKANSAS	*			*	
CALIFORNIA	*	*	*	*	
COLORADO	*	*		*	*
CONNECTICUT	*	*		*	
DELAWARE	*			*	
FLORIDA	*			*	*
GEORGIA	*			*	*
HAWAII	*	*		*	
IDAHO				*	
ILLINOIS		*		*	
INDIANA	*	*		*	
IOWA				*	
KANSAS				*	
KENTUCKY				*	
LOUISIANA	*			*	*

STATE	Disclosures of Medical Information Permitted for Research		State Laws for Human subjects Protection	Conditions Imposed on Genetic Testing/ Genetic Information	Genetic Information Defined as Personal Property
	For Anonymous Data (or Identity Protected)	With IRB Approval or When Federal Rules Apply			
MAINE	*	*		*	
MARYLAND	*	*	*	*	
MASSACHUSETTS				*	
MICHIGAN		*		*	
MINNESOTA				*	
MISSISSIPPI					
MISSOURI	*	*		*	
MONTANA		*		*	
NEBRASKA		*		*	
NEVADA	*			*	
NEW HAMPSHIRE		*		*	
NEW JERSEY	*			*	
NEW MEXICO	*			*	
NEW YORK		*	*	*	
NORTH CAROLINA		*		*	
NORTH DAKOTA	*	*		*	
OHIO	*	*		*	
OKLAHOMA	*	*		*	
OREGON	*			*	

STATE	Disclosures of Medical Information Permitted for Research		State Laws for Human subjects Protection	Conditions Imposed on Genetic Testing/ Genetic Information	Genetic Information Defined as Personal Property
	For Anonymous Data (or Identity Protected)	With IRB Approval or When Federal Rules Apply			
PENNSYLVANIA					
RHODE ISLAND	*	*		*	
SOUTH CAROLINA	*			*	
SOUTH DAKOTA				*	
TENNESSEE	*			*	
TEXAS	*	*		*	
UTAH	*			*	
VERMONT	*	*		*	
VIRGINIA	*	*	*	*	
WASHINGTON	*	*		*	
WEST VIRGINIA				*	
WISCONSIN	*			*	
WYOMING	*	*		*	

TOOL J INTERNATIONAL POLICIES AND GUIDELINES

PARTIAL LIST OF INTERNATIONAL GUIDELINES AND REGULATIONS FOR THE PROTECTION OF HUMAN SUBJECTS IN RESEARCH:

- CIOMS International Ethical Guidelines⁴⁰
- EU Data Protection Directive⁴¹
- Canadian Tri-Council Policy⁴²
- Indian Council of Medical Research: Guidelines for Preparing Standard Operating Procedures (SOP) for Institutional Ethics Committee for Human Research⁴³
- ICH-GCP-E6 Sections 1-4 (US, Japan, EU)⁴⁴
- Declaration of Helsinki (World Medical Association)⁴⁵
- European Union Clinical Trials Directive⁴⁶
- Council of Europe Convention on Human Rights and Biomedicine⁴⁷
- Australian National Statement on Ethical Conduct in Research Involving Humans⁴⁸

⁴⁰ Council for International Organizations of Medical Sciences (CIOMS). 1993. International Ethical Guidelines for Biomedical Research Involving Human Subjects. Geneva: CIOMS.

⁴¹ Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data

⁴² Medical Research Council, Natural Science and Engineering Research Council, Social Sciences and Humanities Research Council. 1998. Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. Ottawa: Public Works and Government Services.

⁴³ <http://icmr.nic.in/home.htm>

⁴⁴ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). 1996. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice. Geneva: ICH Secretariat, International Federation for Pharmaceutical Manufacturers Association.

⁴⁵ World Medical Association (WMA). Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects (adopted 18th WMA General Assembly, Helsinki, Finland, June 1964; amended: 29th WMA General Assembly, Tokyo, Japan, October 1975; 35th WMA General Assembly, Venice, Italy, October 1983; 41st WMA General Assembly, Hong Kong, September 1989; 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996; and 52nd WMA General Assembly, Edinburgh, Scotland, October 2000). Ferney-Voltaire, France: WMA. Available at www.wma.net/e/policy/17-c_e.html.

⁴⁶ The European Union Directive 2001/20/EC, dated 4 April 2001, is concerned with 'the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human use'. The Directive was published on 1 May 2001 in the 'Official Journal of the European Communities' (L121, pp34-44) and is available on the following website: http://www.europa.eu.int/eur-lex/en/search/search_lif.html

⁴⁷ *ETS No. 164 Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (Oviedo, 4.IV.1997)*

⁴⁸ The Commonwealth Parliament enacted the National Health and Medical Research Council Act 1992. The object of that Act was to establish a national body to pursue activities designed to foster medical and public health research and the consideration of ethical issues relating to health. The NHMRC requires all institutions or organizations that receive NHMRC funding for research to establish a Human Research Ethics Committee (HREC) and to subject all research involving humans, whether relating to health or not and whether funded by the NHMRC or not, to ethical review by that committee. The NHMRC expects the Statement to be used as the standard for that review.

BACKGROUND:

Researchers, repository managers, and IRBs should consider the impact of any foreign regulations when conducting research using samples and data received from foreign site or collaborators, or when sharing samples and data with international institutions or researchers. HHS regulations state that the federal policy for protection of human subjects does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research. 45 CFR 46.101 (g)

Researchers who receive specimens or data from foreign sources or who share specimens and data with collaborators in countries outside the US should be aware that the requirements imposed by U.S. federal regulations for informed consent and IRB review of proposed research are generally similar to those of the International Ethical Guidelines for Biomedical Research Involving Human Subjects which were published in 1993 by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO).

HUMAN SUBJECT PROTECTION AND MEDICAL RESEARCH:

In the area of protection of human rights and individual dignity, the Declaration of Helsinki supports the protection of human subjects of medical research, and the Preamble to the 2000 revision makes reference to “identifiable human material or identifiable data.” However, it is unclear how these principles apply to tissue research.

In Europe, the use of tissue for research purposes has not been explicitly addressed as a component of human subject protection for most of the last century. Legal protection for human subjects in research derives chiefly from the national clinical trials laws that must implement the European Union Directive on Clinical Trials (entered into force May 1, 2004). Note that the laws and regulations relating to use of human specimens and a data differ greatly among European countries.

The Council of Europe (the Council, which is distinct from the EU and includes member states that are not currently part of the EU formulates continent-wide agreements regarding legal and social practices that may be ratified by individual member governments) has developed the Convention on Human Rights and Biomedicine (the so-called Convention of Oviedo) reflecting the principal of individual rights and self-determination in the area of medical research, genetic research, and informed consent. Since April 4, 1997, this convention has been open for signature and ratification by the 43 member states. It entered into force on December 1, 1999 and is binding on those countries that ratified it.

One article of the Convention considers the principle of individual rights and self-determination as they apply to tissue research, requiring an appropriate information and consent procedure for secondary uses of tissue.

The Council has also adopted a Protocol on Biomedical Research which outlines more specific ethical guidance for research involving human subjects, covering informed consent, the protection of persons not able to consent to research, research ethics committees, research in emergency situations, research on persons deprived of liberty, availability of results of research and research in States not party to the Protocol.

In 2002, as a supplement to the Protocol, the Council began developing specific ethical guidance for research involving human biological materials. This document, was approved by the Council of Europe as a Recommendation (REC (2006)4) on March 15, 2006. It provides recommendations to the member states of the Council of Europe and the member states then decide whether and how to implement them. The document addresses a number of issues including ethics review of research using human biological materials, informed consent, post-mortem and commercial use of human biological materials, and the return of research results. It also includes specific provisions regarding the transfer of materials from European member states to other countries. Although U.S. regulations provide many of the same protections contained in this document, there are some key differences that may have an impact on collaborative research between the U.S. and European countries, if the recommendations are adopted by member states.

The Charter of Fundamental Rights of the EU prohibits profit from the human body or any of its part as such.

Other statements and guidelines regarding the ethical use of human biological materials in research were issued by the European Group of Ethics in 1998. The EGE comprises a group of national ethics commissions has issued opinions on Human Tissue Banking and has recommended strict controls for uses of tissue for transplants, emphasizes safety and quality control.

NATIONAL LAWS GOVERNING INFORMED CONSENT AND HUMAN SUBJECT PROTECTION

Several countries have national laws and regulations requiring informed consent or otherwise protecting genetic information and creation of biobanks. In particular, many countries have considered restrictions on commercial uses of human biological materials. In Canada, the Medical Research Council has issued standards and procedures governing human subjects research. A statement developed by the Council includes a section addressing the use of human tissue in research, focusing on issues of privacy and confidentiality, free and informed consent, and secondary uses of tissue.

INDIVIDUAL PRIVACY AND CONFIDENTIALITY OF DATA: THE EU DATA PROTECTION DIRECTIVE

The European Union relies on comprehensive legislation that requires creation of government data protection agencies, registration of data bases with those agencies, and in some instances prior approval before personal data processing may begin.⁴⁹ The use and transfer of patient data (including patient data associated with tissue samples) is covered by the European Union (EU)

⁴⁹ On May 1, 2004, ten new Member States formally joined the European Union (EU). These nations are Cyprus, the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia and Slovenia. As a result, EU legislation, including the EU Data Protection Directive (Directive 95/46/EC), as well as the adequacy finding for the U.S.-EU Safe Harbor framework, are now binding upon the new Member States.

Data Protection Directive. The Directive ensures the protection of individuals with regard to the processing of personal data (including sensitive data) and the free movement of such data. According to the Directive, EU member states are obligated to protect the fundamental rights and freedoms of natural person with respect to the processing of personal data and sensitive data.

The European Commission's Directive on Data Protection went into effect in October, 1998, and would limit cross-border transfers of data to countries that provide an adequate level of protection. The Directive could have significantly hampered the ability of U.S. companies to engage in many trans-Atlantic transactions. The EU Commission has the power to determine, on the basis of Article 25(6) of directive 95/46/EC whether a third country ensures an adequate level of protection by reason of its domestic law or of the international commitments it has entered into.

Currently, personal data can flow from the fifteen EU member states and three associate member countries (Norway, Liechtenstein and Iceland) to that third country without any further safeguard being necessary. The Commission has so far recognized Switzerland, Hungary, the US Department of Commerce's Safe harbor Privacy Principles, Canada and Argentina as providing adequate protection.

The U.S. Department of Commerce, in consultation with the European Commission, developed a "safe harbor" framework. The safe harbor — approved by the EU in July of 2000 establishes a means for US companies to obtain certification regarding the adequacy of their data protection. Certifying to the safe harbor will assure that EU organizations know that your company provides "adequate" privacy protection, as defined by the Directive.

FOR MORE COMPLETE INFORMATION

The Department of Health and Human Services Office of Human Research Protection has compiled a listing of the laws, regulations, and guidelines that govern human subjects research in many countries around the world, including those related to human specimen banking and human biological materials (See listing of International Compilation of Human Subject Research Protections on the OHRP website at <http://www.hhs.gov/ohrp/international>).