

Department of Health and Human Services

**OFFICE OF
INSPECTOR GENERAL**

**BIOSPECIMEN RESEARCH:
MEETING BASIC HUMAN
SUBJECTS PROTECTION
REQUIREMENTS AND
COMMUNICATING
INFORMATIONAL RISKS**



**Stuart Wright
Deputy Inspector General for
Evaluation and Inspections**

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EXECUTIVE SUMMARY – BIOSPECIMEN RESEARCH: MEETING BASIC HUMAN SUBJECTS PROTECTION REQUIREMENTS AND COMMUNICATING INFORMATIONAL RISKS

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WHY WE DID THIS STUDY

A biobank is a repository of biospecimens—and, in some cases, associated personally identifiable information (PII) and personal health information—to be used for research purposes. This research must comply with Federal regulations governing human subjects research. An institutional review board (IRB) must review and approve the research, and the principal investigator (PI) must obtain informed consent from all potential subjects unless the IRB waives the requirement for informed consent. In addition, informational risks (i.e., risks related to PII or personal health information), such as a breach of privacy, are magnified because of the long-term electronic storage of the subjects' PII and the potential for the biospecimens to be used in research not specified at the time of collection. Researchers and bioethicists have identified human subjects' potential loss of privacy and confidentiality as a challenge to research that involves biospecimens.

HOW WE DID THIS STUDY

We reviewed 71 studies at 32 institutions that met our inclusion criteria. We assessed relevant informed consent documents and IRB documents for compliance with certain requirements for human subjects protections, as well as additional measures contained in these documents to address informational risks. We also surveyed PIs and IRBs from the institutions that conducted the research.

WHAT WE FOUND

Informed consent documents for biospecimen research contained required information on human subjects protections, but varied in their substance and form. IRBs met basic requirements for membership and continuing review. Some IRBs and PIs took steps to address the informational risks of collecting biospecimens and storing them for future research. IRBs and PIs identified challenges in conducting and overseeing research involving biospecimens, such as determining how much information to share with human subjects, determining how biospecimens should be stored for future use, and dealing with the slow pace of change for regulations governing this type of research.

WHAT WE RECOMMEND

We recommend that the Office for Human Research Protections (OHRP) provide a forum to IRBs and PIs for discussing informational risks to human subjects. OHRP concurred with our recommendation.

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OBJECTIVES

For research that includes the collection of biospecimens, to determine the extent to which

1. informed consent documents comply with human subjects protection regulations,
2. Institutional Review Boards (IRBs) comply with regulations, and
3. principal investigators (PIs) and IRBs take measures to address informational risks (i.e., risks related to human subjects' personally identifying information (PII) or personal health information).

BACKGROUND

Biospecimens, which include blood, plasma, biofluids, and tissue, are biological materials that are taken from human subjects enrolled in clinical research or that remain from a clinical procedure. Biospecimens may be collected and used for a specific study or stored in a biobank for specified or unspecified future research. When stored in a biobank, biospecimens may also include associated PII and personal health information.

According to Federal regulations governing the protection of human subjects, research involving PII about living human beings is considered human subjects research. Research with biospecimens that are labeled with PII is also considered human subjects research. In most instances, to comply with Federal regulations for human subjects research, an IRB must first approve the research protocol and informed consent document, then investigators must obtain informed consent from all potential subjects unless an IRB has waived the requirement for informed consent.¹

Historically, human subjects in research have been exposed primarily to physical risks, such as an adverse reaction to an experimental drug. With biospecimen research, informational risks, such as a breach of privacy, are magnified because of the long-term electronic storage of the subjects' PII and the potential for the biospecimens to be used in research not specified at the time of collection. Informational risks include the improper use of subjects' personal health information or PII to deny health insurance, life insurance, or employment.² The undesired disclosure of research results to

¹ 45 CFR § 46.109.

² The Genetic Information Nondiscrimination Act of 2008 (P.L. 110-233, 122 Stat. 881) prohibits employment and health care discrimination under certain conditions.

subjects, such as the discovery that an individual is genetically predisposed to a disease, is also an informational risk. Without adequate informed consent, subjects may not understand the potential for their biospecimens to be used in unspecified future research to which they may object.³ One such example is the case of the cancerous tissue removed from Henrietta Lacks over 60 years ago. Processing the tissue led to production of the HeLa cell line and provided genetic information, including the predisposition to certain diseases on the part of her descendants.⁴

Public Responsibility in Medicine and Research (PRIM&R), an association of medical researchers, including private-sector experts and Federal officials, that promotes research ethics, has identified human subjects' potential loss of privacy and confidentiality (i.e., informational risks) in research that uses biospecimens as a challenge to this type of research.⁵ The report also raised concerns about the oversight mechanisms for human subjects research, including the lack of a comprehensive regulatory framework that addresses biospecimen storage and use.⁶

Federal Regulations and Guidance for Human Subject Protections

The Public Health Service Act requires the Department of Health and Human Services (HHS) to establish an oversight system for all HHS-supported or HHS-conducted research to ensure that the rights of human subjects are protected.⁷ HHS's Office for Human Research Protections (OHRP) provides clarification and guidance to researchers, IRBs, and institutions on complying with regulations for protecting human subjects while conducting HHS-supported or HHS-conducted research.⁸

The regulations define "research" as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."⁹ A human subject is a living individual about whom an investigator conducting research obtains

³ The Havasupai Tribe of Arizona successfully sued the University of Arizona for using tribe members' blood samples for research on schizophrenia and depression, among other things, without their consent. See A. Harmon, "Indian Tribe Wins Fight to Limit Research of Its DNA," *The New York Times*, April 21, 2010.

⁴ Rebecca Skloot, *The Immortal Life of Henrietta Lacks*, Crown Publishers, 2010.

⁵ PRIM&R, *Human Tissue/Specimen Banking Working Group, Part 1, Assessment and Recommendations*, March 2007, p. 16. Accessed at www.primr.org on August 7, 2013.

⁶ *Ibid.*, p. 7.

⁷ 42 U.S.C. 289(a).

⁸ OHRP, *OHRP Mission Statement*. Accessed at www.hhs.gov/ohrp on August 12, 2013.

⁹ 45 CFR § 46.102(d).

(1) data through intervention or interaction with the individual or
(2) identifiable personal information.¹⁰ No current regulations address the unique risks associated with research that includes the collection of human biospecimens.

IRBs. An IRB is a committee set up to ensure the protection of the rights and welfare of human subjects. Research sites must have an IRB, which has the authority to approve, disapprove, or recommend modifications to proposed research.¹¹ Among other requirements, IRBs must have at least five members, and they must conduct continuing review of research at least annually or more frequently on the basis of an assessment of the research's risk.^{12,13}

Informed Consent. Federal regulations require PIs to obtain informed consent from human subjects before they are enrolled in a study unless a waiver of consent has been obtained. Informed consent must be obtained under circumstances that provide prospective subjects the opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. Informed consent documents must describe the nature and purpose of the research; state the foreseeable risks arising from the study; describe the extent, if any, to which confidentiality of records identifying the subject will be maintained; and state that participation in research is voluntary.¹⁴ IRBs may require that informed consent documents include additional information, should the IRBs determine that the information would provide additional protections to the subjects.¹⁵

Tiered consent and broad consent are two examples of informed consent models used for biospecimen research seeking consent for unspecified future use of subjects' biospecimens. Tiered consent includes options for subjects to decline inclusion of their biospecimens in specific types of future research. The broad consent model simply asks subjects to consent to all future research.¹⁶

The regulations allow for several exemptions from the requirements for informed consent and IRB review. One such exemption is for research

¹⁰ 45 CFR § 46.102(f).

¹¹ 45 CFR § 46.109(a).

¹² 45 CFR § 46.107(a).

¹³ 45 CFR § 46.109(e).

¹⁴ 45 CFR § 46.116.

¹⁵ 45 CFR § 46.109(b).

¹⁶ NCI and Office of Biorepositories and Biospecimen Research, *NCI Best Practices for Biospecimen Resources*. Accessed at www.biospecimens.cancer.gov on August 9, 2013.

involving previously collected information or biospecimens from which identifiers have been removed.¹⁷ In these instances, the research is not considered research on human subjects and, therefore, the requirement to obtain informed consent is waived.

The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. The HIPAA Privacy Rule protects the privacy of individually identifiable health information.¹⁸ The rule applies both in research and health care settings and applies to “covered entities,” including researchers who work within the entities.¹⁹ Researchers may meet Privacy Rule requirements by (1) removing PII, (2) obtaining authorization from the subject, or (3) obtaining a waiver from an IRB or another institutional board established solely to address privacy issues.²⁰

Certificates of Confidentiality. The Public Health Act authorizes NIH to grant Certificates of Confidentiality to research institutions so that they and their researchers may not be compelled by any court to provide any identifying information about an individual enrolled in a study.²¹

NIH

NIH is the largest Federal funder of health research. Of the 27 NIH institutes and centers, 24 make awards that support basic and clinical research, research center operations, scientific training and fellowships, and construction projects. Fiscal year (FY) 2012 expenditures for extramural research awards, which funded research performed by non-Federal scientists using NIH money, totaled \$21.5 billion.²² Some portion of NIH-funded research includes collecting and storing biospecimens, but the size of that portion is unknown.

¹⁷ 45 CFR § 46.101(b)(4).

¹⁸ Social Security Act, §§ 1171–1179, as modified by P.L. 104-191 §§ 104 and 106.

¹⁹ “Covered entities” are defined as (1) health plans, (2) health care clearinghouses, and (3) health care providers that electronically transmit any health information in transactions for which HHS has adopted billing. See 45 CFR § 160.102(a).

²⁰ 45 CFR §§ 164.502(d), 164.508(a)(1), 164.510, 164.512(i).

²¹ NIH, Grants and Funding: *Certificates of Confidentiality: Background Information*. Accessed at <http://grants.nih.gov/grants/policy/coc/background.htm>.

²² NIH, *NIH Data Book – Research Grants: Funding by Institute/Center*. Accessed at NIH.gov on March 28, 2013.

Biobanks and Cancer Research at the National Cancer Institute

Part of NIH, the National Cancer Institute (NCI) is the principal Federal agency for cancer research and training.²³ As part of its responsibilities, NCI awards and monitors grants related to the National Cancer Program. In FY 2012, NCI issued over 6,000 research grants worth about \$3.1 billion.²⁴

Biospecimens are commonly used in cancer research because they contain cellular, molecular, genetic, and chemical information that helps scientists understand the biology of cancer. Through this understanding, scientists can identify characteristics of cancer that can be targeted by a new generation of cancer therapies.²⁵

Genomics is the study of the functions and interactions of genes in a genome.²⁶ The study of human genomics has led to better understanding of the role of genetics in cancer and the development of targeted and more efficient treatment. Further advances in this field depend, in part, on researchers' access to genetic material stored in biobanks.²⁷

Recent Developments

Reviews of IRB practices related to research have found that they fell short of protecting human subjects and communicating potential risks.^{28, 29}

In an effort to update its rules for human subjects protection to reflect current research practices, the Department published an advanced notice of proposed changes to the rules in July 2011.³⁰ The proposed changes included, among other things, (1) determining a format for streamlining

²³ NCI, *NCI Mission Statement*. Accessed at <http://www.cancer.gov/aboutnci/overview/mission> on October 24, 2013.

²⁴ NIH, *Table #106, NIH Grants and Contracts Number of Competing and Noncompeting Awards and Funding Mechanism and NIH Institutes/Centers Fiscal Years 2002–2011*. Accessed at www.report.nih.gov on March 1, 2012.

²⁵ NCI and Office of Biorepositories and Biospecimen Research, *NCI Best Practices for Biospecimen Resources*.

²⁶ A genome is an organism's complete set of DNA, including all of its genes. Definition taken from NIH.gov. Accessed on August 22, 2013.

²⁷ A.E. Guttmacher and F.S. Collins, "Genomic Medicine—A Primer." *New England Journal of Medicine*, 2002; 347:1512–1520, November 7, 2002.

²⁸ Institute of Medicine, *The Common Rule and Continuous Improvement in Health Care: A Learning Health System Perspective*, October 2011. Accessed at www.iom.edu on January 31, 2012.

²⁹ OIG, *IRBs: A Time for Reform*, OEI-01-97-00193, June 1998.

³⁰ 76 Fed. Reg. 44512–44530 (July 26, 2011). See also OHRP, *OHRP Regulatory Changes in ANPRM*. Accessed at <http://www.hhs.gov/ohrp/humansubjects/anprmchangetable.html> on October 28, 2013.

informed consent documents so that subjects providing biospecimens may opt in or out of future research and (2) establishing universal data-security measures similar to those found within HIPAA.³¹

In October 2012, the Presidential Commission on the Study of Bioethical Issues released a report highlighting privacy concerns associated with whole-genome sequencing. The report emphasized the continued benefit of advances in genomic sequencing for society, but also raised concerns about privacy, the potential misuse of information, and unanticipated results reported to subjects from future research. Although the report concentrated on whole-genome sequencing, the Commission's findings and recommendations were also directed more broadly at large research projects that use genetic data.³²

In January 2013, a study from the Massachusetts Institute of Technology's Whitehead Institute highlighted vulnerabilities with stored biospecimens by using publicly available data to identify previously de-identified subjects enrolled in a genomic sequencing study.³³

After genetic researchers mapped the genome for the HeLa cell line and made the information public in March 2013, the family of Henrietta Lacks raised concerns about its privacy.³⁴ In August 2013, NIH responded to these concerns by providing the Lacks family with some control over how the genomic data would be used in future research. The series of events highlighted the need for broader policy addressing privacy of human subjects enrolled in research involving biospecimens, as well as that of their families, and the importance of communicating the potential commercial aspects of the research to human subjects.³⁵

METHODOLOGY

Scope

We reviewed 71 studies (at 32 institutions) that (1) either were active in 2012 or were completed in 2011, (2) were funded by NCI extramural

³¹ 76 Fed. Reg. 44515 (July 26, 2011).

³² The Presidential Commission for the Study of Bioethical Issues, *Privacy and Progress in Whole Genome Sequencing*, October 2012. Accessed at <http://www.bioethics.gov> on April 23, 2013.

³³ M. Gymrek, A.L. McGuire, D. Golan, E. Halperin, and Y. Erlich, "Identifying Personal Genomes by Surname Inference," *Science*, Vol. 339, January 18, 2013.

³⁴ J.J.M. Landry et al., "The Genomic and Transcriptomic Landscape of a HeLa Cell Line," *Genes Genomes Genetics*, March 2013. Accessed at g3journal.org on August 13, 2013.

³⁵ Carl Zimmer, "A Family Consents to a Medical Gift, 62 Years Later," *The New York Times*, August 7, 2013.

grants or cooperative agreements, (3) were human subjects research as defined by regulations, and (4) involved the collection of biospecimens. We used ClinicalTrials.Gov, an NIH-maintained registry of federally and privately supported clinical research studies, to identify the 71 studies in our review. Because information on biospecimen collection is not systematically gathered, we identified the clinical trials in our review through an optional database field indicating biospecimen retention.

Our initial inquiry identified 86 studies, 10 of which were waived from the requirements for human subjects research and therefore did not have informed consent documents. We excluded five others that did not meet our inclusion criteria.

We assessed informed consent documents and IRB documents for compliance with certain requirements for human subjects protections.

Our analysis of the informed consent documents focused on the following four basic required elements:

- a statement of the nature and purpose of the study;
- a description of any reasonably foreseeable risks or discomforts to the subjects;
- a statement describing the extent, if any, to which confidentiality of records identifying the subjects will be maintained; and
- a statement that participation is voluntary.³⁶

Our evaluation of IRBs focused on three requirements:

- that IRBs have at least five members,
- that IRBs conduct initial review of research, and
- that IRBs conduct continuing review of research at least annually or more frequently on the basis of research risk.

Data Sources and Collection

Research Protocol and Informed Consent Documents. We requested the research protocol, informed consent documents, and IRB chairperson's contact information from the PI of each of the 71 studies in our study population. We received all the protocols and informed consent documents that we requested.

³⁶ 45 CFR § 46.116.

IRB Documents. We requested IRB rosters, as well as documentation of both initial and continuing review from the IRB chairpersons overseeing the studies in our study population. Where institutions had multiple IRBs for different types of research, we reviewed only the IRB responsible for overseeing the study in question. We received IRB rosters from 31 of the 32 institutions in our population, documentation of initial review from 68 of the 71 studies in our population, and documentation of continuing review for 70 of the 71 studies.

Survey of Principal Investigators. We surveyed the PIs conducting the studies in the population. We contacted the PIs by email and included a link to an online questionnaire. This questionnaire addressed PIs' training on human subjects protections and on institutional policies and resources for collecting and storing biospecimens; the guidance that PIs have used in these areas; and their experiences conducting this type of research. Additionally, we asked about their perceptions of this type of research and challenges they experienced in conducting it. We sent the questionnaire to 76 PIs for whom we had email addresses.³⁷ Sixty PIs completed the questionnaire.

Survey of IRB Chairpersons. We surveyed IRB chairpersons overseeing the studies in the study population. We contacted them by email and included a link to an online questionnaire. The questionnaire addressed training and guidance related to human subjects protections and the IRB chairpersons' experiences overseeing research that includes collecting and storing biospecimens. We also asked about challenges in overseeing this type of research. We sent the questionnaire to 47 IRB chairpersons at the 32 institutions in the study population. Thirty-two chairpersons from twenty-four unique institutions completed the questionnaire.

Interviews With Representatives From Research Institutions. We interviewed PIs, IRB chairpersons, and other research personnel at two institutions. We chose the institutions because both are large, well-known cancer research institutions.

Analysis

We analyzed the informed consent and IRB documents to determine whether they met requirements for human subjects and how they addressed unique issues associated with this type of research, such as

³⁷ At the time we sent the questionnaire, we had 76 studies in our study population. Five studies were eliminated at a later date because we determined that they did not meet our inclusion criteria.

informational risks, future research, and sharing research results with human subjects.

Limitations

Our ability to identify studies that met our criteria was limited by the extent to which ClinicalTrials.Gov included optional, self-reported data.

We did not determine whether IRBs met the requirement for expertise. Instead, we described measures IRBs took to meet that requirement.

Finally, we did not independently verify the data PIs and IRB chairpersons reported to us in the survey.

Standards

This study was conducted in accordance with the *Quality Standards for Inspection and Evaluation* issued by the Council of the Inspectors General on Integrity and Efficiency.

FINDINGS

Informed consent documents for biospecimen research contained required information on human subjects protections, but varied in their substance and form

All 71 informed consent documents described the nature and purpose of the research, generally at the beginning of the documents. In some instances, the descriptions of the research appeared as bulleted text; in other instances, the descriptions contained additional detail (sometimes extending to several pages) and included scientific language. (For examples of the two different types, see Figure 1.)

Figure 1: Examples describing nature and purpose of research, taken from two informed consent documents

<p>Example 1 This research has three components:</p> <ul style="list-style-type: none">• the collection of tissue samples for research purposes• the use and sharing of data about you and your transplant to improve outcomes• permission to follow you lifelong regarding your health and well-being <p>Example 2 You are being asked to participate in a research study to look at the levels of certain enzymes (proteins that are made by the body to limit or prevent changes in the makeup of the body's cells), as well as oxidative DNA damage (changes to the body's DNA when the cells are deprived of oxygen). DNA is the repository of hereditary characteristics such as what color of eyes a person will have. These changes in proteins and DNA occur in all people over their lifetimes, but are more pronounced in some people than in others. This study will measure some of these changes in subjects who are considered at high risk for developing prostate cancer due to certain existing conditions, compared with subjects who are considered healthy.</p>
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Source: OIG analysis of informed consent documents, 2013.

In all instances, protecting patient information and maintaining confidentiality appeared in clearly marked sections of the informed consent documents. The level of detail in some forms described steps that would be taken to protect participants, such as coding or encryption. Other forms cited HIPAA and indicated how that law applies or contained its relevant language. (For examples of the language on protecting confidentiality, see Figure 2.)

Figure 2: Examples of Language on Protecting Confidentiality

Example 1

Your specimen, information from the specimen, and your medical information will be distributed to researchers at this or other institutions labeled with a unique laboratory code number. Your personal identifying information will not be sent to other researchers. Only the Principal Investigator and their research staff will have access to the link between the code and your name. You will sign a separate HIPAA authorization form for review of your medical records information by Tissue Procurement personnel who are trained to maintain strict confidence. All information obtained by [institution name] is stored and released under conditions designed to protect the privacy of study participants.

Example 2

Your protected health information will be protected according to state and federal law. However, there is no guarantee that your information will remain confidential, and it may be re-disclosed at some point.

Example 3

Your identity will be kept as confidential as possible as required by law. Except as required by law, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier. Your research records may be disclosed outside of [institution name], but in this case, you will be identified only by a unique code number. Information about the code will be kept in a secure location and access limited to research study personnel.

Source: OIG analysis of informed consent documents, 2013.

All informed consent documents included some description of risk and discomfort. However, studies that included the noninvasive collection of biospecimens listed fewer physical risks because they simply followed the subjects' health over time and did not involve additional medical intervention or collection of biospecimens. Other studies included biospecimen retrieval, such as cancerous lung tissue, that required a procedure for removal and had greater physical risks. Informed consent documents for genetic research that did not require a procedure to collect the biospecimens listed lower physical risks. (See Figure 3 for examples of informed consent documents' descriptions of risk and discomfort.)

Figure 3: Examples of Language on Risks and Discomfort

Example 1

Some questions in the questionnaire may be sensitive. You may refuse to answer any questions that make you feel uncomfortable. Participants who have concerns after completing this questionnaire are encouraged to contact their physician or the study doctor.

Example 2

Infection and/or bleeding are always possible when the skin is broken About 1% of patients have serious problems from an internal biopsy. These problems include internal bleeding which may require a blood transfusion or surgery to correct, a collapsed lung, injury to the intestines, gallbladder or kidneys, and infection of the abdominal cavity. You may have an allergic reaction to the numbing medicine. This reaction may be mild, such as a skin rash, or you may have more severe symptoms like throat tightness, low blood pressure, and it may be hard to breathe. In rare cases, a severe reaction could cause death.

Example 3

The greatest risk is breach of confidentiality.

Source: OIG analysis of informed consent documents, 2013.

Finally, all informed consent documents stated that participation was voluntary. Some communicated at the beginning of the document that the research was voluntary. In these instances, the documents often stated that the subject was being asked to enroll in research and could withdraw at any time. In other documents, the statement that the research was voluntary directly followed a description of the nature and purpose of the research. Other informed consent documents contained a separate section that addressed the voluntary nature of the research. (For examples of the language regarding the voluntary nature of the research, see Figure 4.)

Figure 4: Examples of Informed Consent Language Regarding Voluntary Nature of Research

Example 1

You are being asked to take part in a research study. To join the study is voluntary. You may refuse to join, or you may withdraw your consent to be in the study, for any reason.

Example 2

DO I HAVE TO TAKE PART IN THE STUDY?

The choice to take part in this study or not is yours. Make your choice based on what we have explained to you and what you have read about the study.

Taking part is completely voluntary and up to you.

Source: OIG analysis of informed consent documents, 2013.

IRBs met basic requirements for membership, initial review, and continuing review

We received 31 IRB rosters from 32 institutions in the study population, and all of those met the minimum requirement of 5 members. The number of members reached as high as 40 and averaged 17 members.

We received documentation of initial review for 68 of the 71 studies in the population of continuing review for 70 of the 71 studies. All of those met the minimum requirement for continuing review. Twenty-six of thirty-two IRB chairpersons who responded to our survey reported taking additional measures to protect human subjects during continuing review. These measures include updating informed consent documents as new risks arose, auditing logs that document how biospecimens were shared, and conducting routine site visits to ensure that biospecimens were being used according to the IRB-approved protocol.

IRB chairpersons who responded to our survey and those we interviewed provided information on how their IRBs address the requirement for expertise of their members. It is up to each IRB to determine its operating structure to ensure that members have expertise for reviewing research. All the chairpersons who responded to our survey said that they require members to receive training on human subjects protection. Some IRBs use subcommittees to address different types of research, such as biomedical research. Others seek out expertise that may be lacking within the IRB. For example, one IRB chairperson we interviewed told us that he consults with information technology (IT) staff on a case-by-case basis when informational risks to subjects are elevated because of storing PII, rather than having someone with such expertise as a permanent part of the committee. Another chairperson reported integrating an IT risk assessment as a formal part of his IRB's review process.

In addition, 25 of 32 IRB chairpersons who responded to our survey reported that their IRBs require members to attend training on informational risks. Six respondents said that the IRB itself provides educational opportunities both for IRB members and investigators on topics related to informational risk, as well as on administering informed consent. Four respondents said they developed guidance specifically for investigators conducting biospecimen research and IRB members overseeing such research. The guidance these respondents developed includes guidelines for conducting biospecimen and genetic research, conducting genome-wide association studies, and determining what to disclose in informed consent documents for genetic research.

Some IRBs and PIs took steps to address the informational risks of collecting biospecimens and storing them for future research

IRBs and PIs both play important roles in communicating informational risks as the informed consent documents are developed, reviewed, and approved. This process starts during the initial review, when the IRB reviews the study protocol and informed consent document and requests modifications, if appropriate. Our analysis of the 68 initial review documents demonstrates that at times, IRBs recommended modifications to the informed consent documents. These modifications varied and included clarification on how biospecimens would be stored and used in the future and when it might be appropriate to contact the relatives of a subject diagnosed with cancer (see Figure 5).

Figure 5: Example of IRB-Requested Modifications to Informed Consent During Initial Review

Example 1

Revise the [informed consent document] and/or protocol and Abstract to clarify whether agreement to donate residual tissue is an eligibility requirement or an option. It cannot be both.

Example 2

The [relevant committee] recommended that you review the consent form under reference, in particular the risks of genetic counseling.

Source: OIG analysis of informed consent documents, 2013.

Almost all IRB chairpersons—32 of 33—stated that they had required modifications to a research protocol to address these informational risks. Further, 24 of 60 PIs reported that IRBs had required changes to their study documents.³⁸

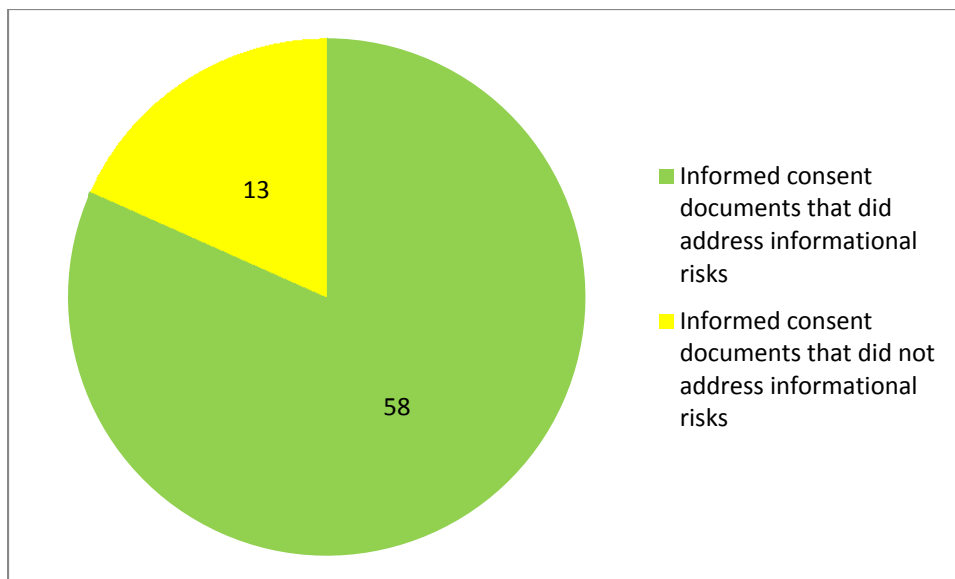
Informational risks to subjects were included in 58 of the 71 IRB-approved informed consent documents

Fifty-eight of the seventy-one IRB-approved informed consent documents described informational risks associated with biospecimen research, including breaches of confidentiality and the consequences and learning potentially sensitive results from genetic research (see Figure 6). These risks generally appeared within the sections of the informed consent

³⁸ The term “study documents” refers to the research protocols and informed consent documents.

documents addressing nature and purpose of the research or the sections addressing physical risks and discomforts.

Figure 6: Informational Risks Addressed in Informed Consent Documents (n=71)



Source: OIG analysis of informed consent documents, 2013.

The long-term storage of biospecimens and their associated data may heighten the risk of a breach of confidentiality. For example, a breach could involve unauthorized access to personal health information; loss or misplacement of data-storage devices, such as laptop computers; or the interception of private information transmitted over the Internet.

Breaches could result in human subjects' information being used against them, and 52 of the 71 informed consent documents discussed this risk. For example, the potential exists for genetic information to be used to deny health insurance or life insurance or to claim or deny paternity. Figure 7 shows how one IRB-approved informed consent document informs human subjects of this risk.

Figure 7: Example Describing the Consequences of a Breach of Confidentiality

The greatest risk of sharing your genetic information is the possible loss of your privacy. Although no identifiable (name, address, etc.) information will be given to the National Institutes of Health (NIH, the federal government agency that stores genetic information), the possibility exists that your genetic information may be taken, used for reasons outside of this project, and in the future be used to identify you. If your genetic information is linked back to you in the future, it may be used by employers and insurance agencies to discriminate against you, or by law enforcement to link you, or one of your family members, to a crime.

Source: OIG analysis of informed consent documents, 2013.

Biospecimen research also could identify sensitive results from a genetic test. Disclosing this information may be undesirable or upsetting to a human subject. An example of such a risk is learning that one has a genetic predisposition to Alzheimer's disease but can do nothing to decrease the chances of developing it. Twenty-one of the informed consent documents we reviewed indicated that research results may be shared with subjects. Of those, 6 indicated that research results would be shared with the subjects unconditionally; the other 15 indicated that results would be shared with the subject only under certain conditions, such as the receiving of genetic counseling by the subject.

In some cases, informed consent documents described legal protections designed to protect subjects (see Table 1). For example, 18 of the 71 informed consent documents described certificates of confidentiality. These informed consent documents described potential consequences of releasing private information to an employer or insurer and the ways in which a certificate protects subjects from that risk. Similarly, 13 of the 71 informed consent documents describe how the Genetic Information Nondiscrimination Act protects individuals from inappropriate use of their genetic information.

In other cases, the informed consent documents disclosed how research on the collected biospecimens might lead to commercial products. For example, 37 of 71 informed consent documents addressed the potential for a commercial product while also stating that the subjects would not receive any financial benefit.

Table 1: Informational Risks and Related Issues Addressed in Informed Consent Documents

Issue Addressed	Number of Informed Consent Documents*
Informational Risks (in General)	58
Specific Informational Risks Breach of Confidentiality Learning Potentially Sensitive Results from Genetic Research	52 21
Possibility of a Commercial Product with No Financial Benefit for Subject	37
Research Institution Has an NIH-Granted Certificate of Confidentiality	18
How the Genetic Information Nondiscrimination Act Protects Subjects	13

*Each informed consent document may include one or more of these elements.

Source: OIG analysis of informed consent documents, 2013.

About two-thirds of informed consent documents provided human subjects with some control over how their biospecimens would potentially be used

Forty-nine of the seventy-one informed consent documents allowed subjects to select the specific types of research in which they would like to participate, while opting out of other types of research. This approach, called tiered consent, gives human subjects a degree of control over the types of research for which their biospecimens are used. For example, tiered consent might permit one subject to opt in for cancer research but opt out of research on Alzheimer’s disease, while permitting another subject to choose to participate in all types of research. Tiered consent could also include a provision for a subject to indicate whether he/she would like to be contacted about future research. (See Figure 8 for examples of informed consent language under a “tiered consent” framework.)

Figure 8: Examples of Language for Tiered Informed Consent

Example 1
My specimens may be kept for use in research to learn about, prevent, or treat HIV.

Yes ___ No ___

My specimens may be kept for use in research to learn about, prevent, or treat other health problems such as human papillomavirus (HPV) infections and anal or genital cancer.

Yes ___ No ___

Someone may contact me in the future to ask me to take part in more research.

Yes ___ No ___

Example 2
I elect to ___ or not to ___ have leftover blood and tissue specimens stored in a tissue bank for optional studies.
Participant's initials ___

I elect to ___ or not to ___ have the results of any future research disclosed to me.
Participant's initials ___

I elect to ___ or not to ___ provide contact information on the attached page for relatives to be contacted about the study.
Participant's initials ___

Source: OIG analysis of informed consent documents, 2013.

IRBs and PIs identified challenges in conducting and overseeing biospecimen research

In conducting research, PIs and IRBs must balance the competing demands of protecting human subjects and making scientific progress. All respondents seemed to recognize those competing demands. They face challenges in achieving that balance.

First, PIs identified a challenge in determining the level of detail to provide to potential subjects about the various risks associated with participating in biospecimen research. Their concern was that providing extensive detail could deter subjects from participating. Not only can such an explanation be time-consuming, but it also can raise potential subjects' concerns about risks that they might face should they decide to participate. As one principal investigator stated, "[The] primary challenge is recruitment resulting in fewer subjects enrolled than expected. The

informed consent form is long, arduous, and implies greater risk than is realistically present.”

Second, storing biospecimens for future use and controlling access to them also presents challenges, especially for individual PIs. Of the 51 PIs who responded to our question as to who controls distribution of their biospecimens, 23 PIs said they themselves did, 18 said IRBs did, and 4 said the institution’s research management office did. Tracking PII associated with the biospecimens can be handled with a simple spreadsheet or a sophisticated database, but the challenge is ensuring that the PII is secure. In addition, monitoring the distribution and associated level of consent for each biospecimen can be difficult. Furthermore, repositories need emergency alarms and, to safeguard the biospecimens in the event of a power failure, backup power systems. Purchasing and maintaining these systems can be costly, and such costs are borne more easily by institutions than by individual PIs.

Third, the rapid pace of change in biospecimen research and the slower pace of regulatory and policy changes can create uncertainty. One IRB chairperson captured this uncertainty when he told us, “We are left to apply generic regulatory standards to a very specific and often confusing type of research, which can be difficult.” Among the 32 IRB chairpersons who responded to our survey, 8 cited a lack of clarity in Federal regulations as a challenge in overseeing research that includes collecting biospecimens. On the other hand, 55 of 60 PIs responding to our survey stated that regulations clearly articulate what is expected of them as researchers.

CONCLUSION AND RECOMMENDATION

As the field of biospecimen research advances, researchers are using the existing and familiar human subjects protection system to inform human subjects about risks. Overall, our evaluation found that informed consent documents met the basic requirements for human subject protections; in addition, IRBs met basic requirements for membership, initial review, and continuing review.

The majority of informed consent documents addressed the informational risks of biospecimen research. These include breaches of confidentiality and learning about potentially sensitive results from genetic research. The majority of informed consent documents also gave subjects some control over how their information will be used in future research.

Researchers and IRBs involved in biospecimen research are trying to address challenges regarding how much information to share with potential subjects, how to store and share biospecimens, and how to deal with a regulatory system that progresses at a slower pace than scientific research.

Because the field is in flux and the regulatory system moves slowly, the research community has much discretion in determining how to address these challenges. The Department is also working to address challenges with human subjects research protections, having issued an advance notice of proposed rulemaking in July 2011.

In 2012, the Presidential Commission on the Study of Bioethical Issues released a report that raised concerns about privacy, the potential misuse of information, and unanticipated results reported to subjects from future research. More recently, in January 2013, that Commission announced that it would examine what patients and participants are told by health care professionals not only *after* a procedure or a test is performed, but also *before*, as part of the informed consent process.

Determining how to communicate informational risks to human subjects will be a challenge, but doing so effectively will be an important contribution to scientific advancement. To facilitate this process, we recommend that OHRP:

Provide IRB members and investigators with a forum for discussing informational risks to human subjects

Federal regulations require that informed consent documents include a statement of the foreseeable risks arising from the study. Historically, human subjects enrolled in clinical research have been exposed primarily to physical risks, such as an adverse reaction to an experimental drug.

More recently, researchers' ability to collect and store information from biospecimens has raised concerns about informational risks that may arise from clinical research. These risks, such as a breach of privacy, are magnified because of the long-term electronic storage of the subjects' PII and personal health information, and the potential for biospecimens to be used in research not specified—or even envisioned—at the time of their initial collection.

OHRP could help ensure that IRB members and investigators address informational risks in biospecimen research by providing them with a forum for discussing challenges and best practices related to communicating these risks. Considering such risks would help provide additional protections to subjects who enroll in studies that would include the collection and future use of biospecimens. Possible approaches include an online forum, Webinars, an OHRP-sponsored conference, or presentations at other scientific meetings.

AGENCY COMMENTS AND OFFICE OF INSPECTOR GENERAL RESPONSE

OHRP concurred with our recommendation to provide IRB members and researchers with a forum for discussing informational risks to human subjects. It highlighted past efforts as well as plans to provide a forum to discuss informational risks with relevant stakeholders at upcoming regional and national conferences. OHRP also emphasized the informational risks present in research for which IRBs have issued waivers from the requirement to collect informed consent. Although permitted by human subjects regulations, such waivers prevent human subjects from being fully advised of those informational risks.

APPENDIX A

Agency Comments



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Office of the Assistant Secretary for Health
Washington, D.C. 20201

SEP 25 2013

TO: Inspector General

FROM: Assistant Secretary for Health

SUBJECT: OIG Draft Report: *Biospecimen Research: Meeting Basic Human Subjects Protection Requirements and Communicating Informational Risks*, OEI-01-11-00520.

We have received the Office of the Inspector General (OIG) Draft Report entitled *Biospecimen Research: Meeting Basic Human Subjects Requirements and Communicating Informational Risks*, OEI-01-11-00520. The Report focuses on an important feature of the protection of human subjects in research, namely, the communication of informational risks as part of the informed consent process for research studies which include obtaining and analyzing biospecimens. The Report includes a description of a study carried out by the OIG in which the OIG reviewed the informed consent documents and Institutional Review Board (IRB) documents for 71 human subjects research studies that involved the collection of biospecimens and were funded by the National Cancer Institute of the National Institutes of Health. The Report identifies the challenges of providing appropriate protections for the human subjects involved in such research under existing regulations and policy, and focuses on issues related to the appropriate disclosure of informational risks in research involving biospecimens.

We certainly agree that the rapid development of new research technologies creates special challenges related to how informational risks should be disclosed to subjects as part of the informed consent process. At the same time, however, we believe it is important to note that there is a considerable amount of research involving biospecimens where the informed consent of the subjects is never sought, and consequently the disclosure of informational risks does not occur. Part of the explanation for this is that some biospecimen research does not fall under the regulatory requirements of the regulations for the protection of human subjects in research at 45 CFR 46, and consequently there is no regulatory requirement for informed consent. Another part of the explanation is that even where the regulations do apply, the regulations allow for waiver of informed consent. In the circumstance of investigators obtaining biospecimens and identifiable private information from a biobank rather than directly through interaction with individual subjects, we believe that IRBs frequently waive the requirement for informed consent consistent with the regulatory waiver criteria. The OIG study focused only on research studies where there was direct interaction with individual subjects, which provided a natural opportunity to obtain informed consent. The issue of informational risks also arises for biospecimen research where informed consent was not obtained, and we believe that this issue also needs to be taken into consideration for those biospecimen research studies, which may well be a larger part of the research enterprise.

U.S. Public Health Service

Agency Comments (Continued)

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We concur with the OIG Report's recommendation that the Office for Human Research Protections (OHRP) should provide a forum for IRB members and investigators to address informational risks in biospecimen research. Indeed, OHRP has already provided such fora on a number of occasions, and will continue to do so. In March of 2011, the Secretary's Advisory Committee on Human Research Protections (SACHRP) held a panel on the topic of returning individual results to subjects, which is one element of the issue. In October of 2011, SACHRP submitted recommendations titled *FAQs, Terms and Recommendations on Informed Consent and Research Use of Biospecimens*. In October of 2011 SACHRP also included comments related to informed consent and biospecimen research in its comments on the Advance Notice of Proposed Rulemaking of July, 2011 titled *Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators*. We expect that SACHRP will return to this issue in the near future. In October of this year, OHRP will sponsor a webinar titled *Biobanking: When Issues with Tissues Come a Knockin'* as part of its webinar series; these webinars are recorded and are also viewable on YouTube after they happen. And in October the issue will also be addressed as part of the program of an OHRP Research Community Forum titled *Innovative Strategies: Taking the Protection of Human Subjects to the Next Level*, in Nashville, Tennessee. We fully expect other future Research Community Fora to include this topic. And finally, OHRP staff working with the planning committees of the annual meeting of Public Responsibility in Medicine and Research have ensured that this issue will also be part of the program of this year's meeting in November. OHRP will certainly look for other opportunities to advance discussion of this topic as well.

Thank you for the opportunity to comment on the draft Report. Please feel free to contact me if you have any questions.

/s/

Howard K. Koh, M.D., M.P.H.

ACKNOWLEDGMENTS

This report was prepared under the direction of Joyce Greenleaf, Regional Inspector General for Evaluation and Inspections in the Boston regional office, and Deputy Regional Inspectors General Russell Hereford and Kenneth Price.

Christopher Galvin served as the team leader for this study, and Elizabeth Havener served as the lead analyst. Central office staff who provided support include Heather Barton, Althea Hosein, Christine Moritz, and Talisha Searcy.

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