

Wayne State University Human Investigation Committee	
SUBJECT	The Use of Biological Specimens for Research
Section	
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Background

With the increased use of human biological samples from tissue banks and repositories for research purposes, ethical and regulatory dilemmas exist regarding the distribution and use of these materials in research projects. The implications that this has on individuals and families when these samples are used for genetic research increase the regulatory and ethical burdens.

There are three distinct areas of concern in biological specimen research. The first involves genetic studies where the findings might involve risks that could harm an individual, a family, a group or community. These risks could include psychological, social, or economic harm. Examples of this might include an employer or insurance company learning of a genetic predisposition for a particular disorder and refusing employment or coverage. For this type of genetic research, the issues of confidentiality become paramount and the Principal Investigator (PI) should detail the steps that will be taken to prevent the misuse or unauthorized disclosure of the participants' records. Full Board review by the Wayne State University (WSU) Institutional Review Board (IRB) would be required for this type of genetic research protocol.

The second area of biological specimen research involves genetic research where there is very little perceived risk for psychological, social or economic harm to individuals or groups from whom the specimens are derived. In this type of research, the specimens are usually rendered anonymous and the results cannot be linked in any way to individuals or groups from whom they are obtained. An example of this type of research would be anonymous samples of tumor cells being analyzed for specific genetic information. In this case, the PI should detail the steps that will be taken or have been taken to de-identify and render the samples in question anonymous. The method that the IRB would use to evaluate this type of research would vary depending upon the protocol.

The third type of biological specimen research involves non-genetic studies. Although there may be less effect upon perceived risk to the participant, families, groups, and communities, the method that the IRB would use to evaluate this type of research and to determine whether or not informed consent is required would vary depending on the protocol.

Tissue Banks

Tissue banks and specimen repositories are established for a variety of purposes, ranging from clinical evaluation and diagnosis, to the use of discarded materials, or the use of samples collected specifically for research purposes. All of the implications for use of these samples and materials may not have been addressed at the time that the sample was collected and added to the bank or repository. However, it is important to anticipate potential future use of the database and/or repository in order not to limit how that data may be used in research in the future. The prudent step is to submit a protocol for the tissue bank and/or specimen repository to the IRB for review and approval, even if future use of such banks or repositories is not initially known.

Health Insurance Portability and Accountability Act (HIPAA) and Tissue Banks and Data Repositories

Prior to HIPAA, the creation and maintenance of a specimen repository did not require IRB review and approval unless the repository or specimen database was specifically created for research purposes. However, with the advent of HIPAA, the creation and maintenance of a specimen repository or database that may subsequently be used for research must have review and approval from the organization's Privacy Board before that data may be deposited in the repository and/or database. Because the WSU IRBs have been designated as the Privacy Board for the Detroit Medical Center (DMC), all of the WSU Practice Plans, and the John D. Dingell Veterans Administration Medical Center (VAMC), the WSU IRBs must review and approve all repositories or specimen databases that may subsequently be used for research purposes. This Privacy Board review is in addition to the IRB review and approval. In other words, all specimen and data repositories that may be used for research purposes in the future should be reviewed and approved by the WSU IRB for review and approval.

The subsequent use or disclosure of information from any of those specimen databases or repositories is considered a separate research study and would require IRB review and approval at the time of the proposed research use.

Scope

This policy encompasses all cells, cell lines, and tissues that are derived from human beings, deceased or living, with the exception of those derived from the pregnant woman, a viable fetus, and a viable or nonviable neonate. Research in which the subject is a fetus, in-utero or ex-utero (including human fetal tissue) must not be conducted by Veterans Administration investigators while on official duty, or at VA facilities, or at approved off-site facilities. [VHA 1200.5 D.4(a)]

This policy also covers the placenta and umbilical cord, the dead fetus, macerated fetal material, or cells, tissue or organs excised from a dead fetus after delivery [45 CFR 46 Subpart B 206 (a)].

Any research involving the transplantation of human tissues derived from any source into another human being is not covered by this policy.

Definitions

Anonymous Samples - Specimens obtained by an investigator without any identifying information and without a link to a specific individual.

Coded Specimens – Specimens where:

1. Identifiers (see below) have been replaced with a number, letter, symbol, or combination of all and
2. A key to decipher the code exists, enabling the linkage of the code to a specific individual.

Individually Identifiable Samples - Samples obtained by the investigator that have identifiers or a link that permits the determination of the individual participant through the use of a code.

Identifier - Information that could be associated with a specific research participant [name, address, elements of dates, phone numbers, fax numbers, social security number, medical record number, health insurance number, account numbers, certificate or license numbers, vehicle and serial numbers, device ID and serial numbers, WEB URLs, IP Addresses, biometric identifiers (finger prints, full face photographs or comparable images), any unique identification number, characteristics or codes].

Genetic Research - Research that involves either:

1. The analysis of human chromosomes or DNA from an individual and/or family members for the purpose of deriving information concerning that individual or family about the presence, absence or mutation of genes, DNA markers or inherited characteristics; or
2. Other studies with the intent of collecting and evaluating information about inheritable diseases and/or characteristics within a family.

Research –

1. Under DHHS regulations, research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.
2. Under FDA regulations “research” 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 FDA under section 505(i) or 520(g) of the Food, Drugs, and Cosmetics Act, or need not meet the requirements for prior submission to the FDA under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit. For research involving drugs, an experiment is any use of a drug except for the use of market drug in the course of medical practice.

Human Subject (Participant)

1. Under DHHS regulations “human subject” (participant) means a living individual about whom an investigator (whether professional or student) conducting research obtains: (a) data through intervention or interaction with the individual or (b) identifiable private information (about that individual). This may be further defined as follows:

- 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/or 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). The 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 [45 CFR 46.102(f) and 38 CFR 16.102(f)].
2. Under Food and Drug Administration (FDA) regulations human subject (participant) means an individual who is or becomes a subject in research, either as a recipient of the test article or as a control. A subject (human participant) may be either a healthy individual or a patient [(21 CFR 56.102(e)]. For research involving medical devices a human subject is also an individual on whose specimen an investigational device is used.
 3. Because the definitions are different between the Common Rule and the FDA regulations, the IRB must follow the definition used by the agency that regulates the specific research project. Consequently the definition from the Common Rule or the definition used by FDA or a combination of both must be used in a specific research proposal.

Human Participant Research -

1. Meets the Department of Health and Human Services (DHHS) definition of "research" and involves human subjects as defined by DHHS regulations, or
2. Meets the FDA definition of "research" and involves "human subjects" as defined by FDA regulations.

Investigator - Anyone (whether professional or student) involved in the conduct of research.

Delivery - Delivery occurs when there has been complete separation of the fetus from the mother by expulsion or extraction or any other means.

Placenta - is the vascular structure in the uterus of the mother that provides oxygen and nutrients for – and transfers wastes from -- the developing fetus.

Fetus - the products of conception from implantation until delivery [45 CFR 46.202 (c)].

Dead Fetus - A fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles nor pulsation of the umbilical cord.

Neonate (newborn) - refers to the human child from birth to 4 weeks of life.

Viable neonate -- is a neonate that has the ability to survive, after delivery, to the point of independently maintaining heartbeat and respiration, given the benefit of medical therapy, if needed.

Nonviable neonate - refers to a neonate after delivery that, although living, is not viable, i.e. does not have the ability to survive after delivery.

Prospective Study - A study in which the collection of specimens will occur "in the future". In other words, the biological specimen is not "on the shelf" when approval for the research under review is requested. This may refer to:

1. Specimens that will be obtained specifically for research purposes after the research protocol has been approved by the IRB wherein the participant is asked to undergo a procedure to obtain a specimen for research purposes, or
2. Specimens to be collected from discarded clinical samples that will be obtained after the research is approved by the IRB.

Retrospective Study -- A study that utilizes existing specimens that have already been collected when the request for review and approval is made. This may refer to:

1. Tissue collected for clinical indications and then stored (i.e., Pathology specimens, left over serum; or
2. A secondary use of tissue collected previously for another research protocol (material in a tissue bank).

HIC Policy/Procedures

Wayne State University has designated the HIC Chair or his/her designee, as the individual who is authorized to determine whether or not research involving biological specimens constitutes human participant research and may be exempt from IRB review and approval. The institution believes that these individuals are most knowledgeable about the regulations that govern human research participant protection and how it would apply to a specific protocol. When a research protocol is not eligible for exemption from IRB review and approval, the IRB must consider the use of the biological sample in either prospective or retrospective studies or both. See HIC Policy & Procedure: "Exempt Review" at the www.hic.wayne.edu.

For prospective activities requiring IRB review and approval, the study must meet the definition of research at the time that the prospective study is being proposed. During IRB review and approval, the IRB would also make a determination as to when informed consent and HIPAA authorization are required or whether or not a waiver of consent and waiver of HIPAA authorization can be granted.

For retrospective studies, the IRB must also determine if informed consent and HIPAA authorization is required or if a waiver of consent and HIPAA authorization may be granted.

When biological specimens are obtained from a 3rd party, the IRB must determine who has access to the code (identifiers) and whether or not that person is "involved" in the research protocol. If the individual who holds the link to the code is "involved" in the research project, the protocol is not eligible for exemption from IRB review and approval. The WSU IRBs do not consider the act of solely providing coded specimens to constitute involvement in the conduct of research. However, if the individual who provided the samples and who is the only individual to maintain the link to the codes has other study responsibilities (i.e., involved in the design, analysis of data, authorship and/or presentations of result), the individual is considered

“involved” and the protocol must be reviewed and approved by the IRB. When the provider of the coded specimens is not “involved” in the research protocol, a written agreement between the PI and the individual who maintains the link must be submitted to the IRB as part of their review and approval.

Because identifiers are almost always included in the creation of a specimen bank, informed consent and HIPAA Authorization would be required. The specimen bank may be eligible for Expedited Review by the IRB.

Table 1: Retrospective Research involving Previously Stored Biological Specimens

Guide to IRB Requirements

	Genetic and Non-Genetic Research		
Participant Identity	IRB Review	Informed Consent	HIPAA
Anonymous-“No link”	May be Eligible for Exemption ¹	Not Required	Authorization or Waiver Not Required
Link to coded specimens is <u>not</u> provided to research team ²	May be Eligible for Exemption ^{1,2}	May or May not be Required	Authorization or Waiver Not Required
Identifiers known to research team	Expedited or Full Board Review	May or may not be Required	Authorization or Waiver of Authorization <u>may be</u> Required
<p>¹ When the research may result in socio-economic risks to a class of individuals, families, or a particular group, the protocol must receive full IRB review and approval.</p> <p>² For IRB concurrence, a written agreement between the individual holding the link and the research team must be included with the IRB application.</p>			

Policy on the Use of Biological Specimens in Retrospective Studies

1. If specimens obtained for clinical or diagnostic purposes (biological waste and leftover specimens) are to be used for retrospective research studies, then their use in research may be exempted from IRB review or they may require expedited or full board review by the IRB. The same standards would apply if the samples had been collected for research purposes.
2. If the samples are to be used anonymously and the results will not place an individual, family, or a community or cultural group at significant social or economic risk, an investigator may request an exemption from IRB review and approval. No written informed consent or documentation of HIPAA authorization or waiver would be required for these types of research protocols.
3. If the link to identifiers exists but is not provided to the research team, and the results will not place a community or cultural group at significant social or economic risk, an investigator may request an

exemption from IRB review and approval. No written informed consent or documentation of HIPAA authorization or waiver would be required for these types of research protocols. However, there must be a signed written agreement that specifies that the individual holding the code will never make the identifiers available to the research team. Both the individual holding the code and the principal investigator must sign the agreement (See Template for Agreement)

4. If the samples can be linked to identifiers that are known to the research team, the research protocols will be expedited or will require full board review. Either a written informed consent or a request for a waiver of consent and documentation of HIPAA authorization or waiver of HIPAA authorization would be required for these types of research protocols.

Table 2: Prospective Research Studies involving Biological Specimens

Guide to IRB Requirements

	Genetic and Non-Genetic Research		
Participant Identity	IRB Review	Informed Consent	HIPAA
Anonymous-"No link"	Expedited	Not Required	Authorization or Waiver Not Required
Linkage <u>not</u> provided to research team ¹	Expedited ¹	Not Required	Authorization or Waiver Not Required
Identifiers known to research team	Expedited or Full Board Review	Consent or Waiver may be Required	Authorization or Waiver may be Required

¹ For IRB concurrence, a written agreement between the individual holding the link and the research team must be included with the IRB application.

Policy on the Use of Biological Specimens in Prospective Research Studies

1. No prospective studies involving biological specimens qualify for exemption from IRB review and approval.
2. If prospectively collected specimens obtained for clinical or diagnostic purposes are to be used for research purposes, then future use of the specimens in research protocols must be approved by the HIC before the specimens are to be used. Biological waste and leftover specimens are included in this category.
3. If biologic specimens collected prospectively are to be used for genetic research purposes, and the genetic information being collected may place the participant, families, groups or a community at psychological or socio-economic risk, the protocol must have Full Board Review and approval before the specimens can be collected and used in research.
4. If there is no link to the identifiers for the biologic specimens, the research protocol is eligible for expedited IRB review and approval. No written informed consent or documentation of HIPAA authorization or waiver would be required for these types of research protocols.

5. If a link to identifiers exists but is not provided to the research team, the research protocol is eligible for expedited IRB review and approval. No written informed consent or documentation of HIPAA authorization or waiver would be required for these types of research protocols. However, there must be a signed written agreement that specifies that the individual holding the code will never make the identifiers available to the research team. Both the individual holding the code and the principal investigator must sign the agreement.
6. If the biological specimens can be linked to identifiers that are known to the research team, the research protocols will require either expedited or full board review dependent on the type of protocol. Written informed consent or a waiver of consent and documentation of HIPAA authorization or waiver of HIPAA authorization would be required for these types of research protocols.

Policy on Informed Consent for Biological Specimens Research

The regulations governing the consent process for research with human participants described in 45 CFR 46.116-117, 21 CFR 50.25 & 27(a) and 38 CFR 16.116-117 apply to all research protocols involving stored tissue whenever it is necessary to obtain informed consent as deemed necessary by the WSU HIC policies. When the IRB determines that a waiver or alteration of the informed consent may be granted, those regulations that describe specific oversight for that process will be followed [45 CFR 46.116(c) & 117 (c), (21 CFR 56.109(c) and 38 CFR 16.116(c) & 117(c)]. In addition, for the prospective storage of human tissue (banking), the consent form must contain the following information as appropriate to the individual protocol:

1. A description of planned future use of the specimens. If this is unknown, this should be so stated in the consent document.
2. A description of the procedures that will be used to protect the confidentiality and privacy of any personal identifiers that will be associated with the source of a tissue sample or cell line.
3. Information about the control and ownership of the tissue samples during storage.
4. A statement that the participant's right to withdraw his/her consent at any time either by requesting that the tissue be destroyed or that all personal identifiers be removed.
5. Information about the length of storage.
6. A statement about whether the participant can obtain future access to the stored samples for information that may be of clinical relevance to him/her. Similarly, participants must be told if such information will not be available in the future (e.g., because personal identifiers are to be removed.).
7. How the investigator will handle future third-party access.
8. Information about possible secondary use of the stored tissue or the possible creation of an immortalized cell line based on the specimen.

When research after delivery involves the placenta, the dead fetus, or macerated fetal materials such as tissues, cells or organs, and information associated with this material is recorded in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent subparts of this part are applicable [45 CFR 46.206 (a) (b)].

Special Considerations

There may be situations where a patient or research participant is known to possess biologic materials with unique characteristics thought to have potential commercial value. In this case, if specimens are to be collected for research and the investigator expects that the specimens will be commercialized into a marketable product or sent to a commercial sponsor for research or development, the consent form must state this possibility. HIC policy requires that the consent form stipulate that the participants will not have any financial or proprietary interest in the samples or in any products or processes that may result from research on the samples.

References

In August 2005 the Office for Human Research Protections (OHRP)¹ issued guidance on research involving coded private information and human biological specimens. In addition, references to pertinent Health Information Portability and Accountability Act (HIPAA)² Privacy Rule requirements were also included. This document provides direction in the policy and procedures used by Wayne State University's (WSU) Institutional Review Boards (IRBs) in protecting the confidentiality and privacy rights of participants.

¹ www.hhs.gov/horp/policy/index.html#repositories

² <http://privacyruleandresearch.nih.gov/>