

Guidance and Procedures for Investigators

Topic: Research Using Human Biological Materials (Samples)

The use of human biological materials (samples) in research requires review by OPHS and, where appropriate, the IRB. OPHS and the IRB's role is to ensure that research using human samples is conducted in an ethical manner that protects the human subjects from whom the samples were obtained.

Research that utilizes human samples may qualify for Exempt, Expedited, or Full Board review, dependent upon the potential risks the research poses to subjects. This determination is one that must be made by OPHS, not by the investigator. Therefore, faculty and staff should consult with OPHS staff prior to conducting any research that involves human samples.

What is Considered Human Biological Material?

Human biological materials include tissue samples, blood, sputum, urine, bone marrow, and cell aspirates. Many researchers refer to these materials as "samples" or "tissues" in their IRB applications and research protocols. They will be referred to as "samples" throughout this section.

Categories of Samples

Existing Samples

Many research studies involve samples that are retrospective in nature. The archived samples were originally collected for medical/clinical purposes, or they were collected for the establishment of a research tissue repository. These will be referred to as "existing samples." Existing samples may be frozen at the time of collection or preserved in some other manner that allows storage at room temperature for long periods of time, such as paraffin blocks or histologic slide files.

Prospective Samples

Research using human samples may also be prospective in nature, using freshly obtained samples from the human subjects enrolled in the research study. These types of samples will be referred to as "prospective samples."

Unidentified Samples

Unidentified samples may also be referred to as "anonymous" samples. Unidentified samples are collected without direct identifiers. Therefore, personal information was not collected and cannot be retrieved by the investigator or repository. These types of samples involve the lowest level of risk.

Unlinked Samples

Unlinked samples were originally collected with identifiers, however these samples have been “stripped” of these identifiers. Therefore, identifying a person through the demographic or health data associated with the unlinked sample would be very difficult. Unlinked samples may have been stripped of identifiers prior to being received by the investigator or institution. Samples may also become “unlinked” after they are in the possession of the investigator/institution when they are stripped of identifiers by a disinterested (third) party. Unlinked samples may also be referred to as “anonymized” samples.

Identifiable Samples

Identifiable samples are those in which the identity of the person providing the sample can be easily discovered. The federal government considers samples to be identifiable when the sample or related health information/data can be linked to a specific person by the investigator, either directly (name, social security number, or medical record number) or through a unique study identification number, sometimes referred to as a “code.”

Coded Samples

“Coded” samples, often called “linked” samples, are those in which the identifier(s) have been replaced with an identification number or numerical code, and a master list or key that provides a link between the unique identification number and specific person exists. Coded samples are considered to be identifiable samples because they contain a link to the individual.

Evaluating the Level of Risk

The major risk to subjects in research that involves human samples is informational risk (i.e. breach in confidentiality). This level of risk will vary depending upon if the samples are unidentified or identifiable. Research with unidentified samples presents the lowest level of informational risk, and should qualify for Exempt review. Research with unlinked samples is also considered to be low risk, and may qualify for Exempt review as well.

Research with identifiable samples and coded samples will present a greater informational risk to subjects because there is a potential risk of disclosure of demographic or protected health information. This information may be harmful to the subject if it falls into the wrong hands. Potential harms to the subject from a breach in confidentiality include the loss of health insurance or life insurance, loss of employment, or social stigmatization, among others.

When designing a protocol that involves research with samples, investigators should focus on creating an appropriate plan to reduce this informational risk. OPHS recommends that investigators create a section in the protocol titled “Special Precautions.” In this section, investigators should provide a detailed description of how the specimens and related health information will be “stripped” of identifiers, and describe an appropriate sample/data storage and security plan. Another important aspect of evaluating risk in research that uses coded samples is the security of the master list or code key, and the policies that determine when the master list or code key can be accessed or broken. Detail on this should be provided in the protocol synopsis (if applicable) for identifiable samples that are collected at UNTHSC or at outside entities.

Per federal guidelines, research with coded samples may qualify for Exempt review if:

1. The specimens were not collected specifically for the proposed research project described in the IRB application; and
2. If the investigator cannot easily determine who the specimen or related health information belongs to.

This situation may occur if the master list or key to the code was destroyed prior to the submission of the IRB application to OPHS. Additionally, investigators may enter into an agreement with the entity or individual who holds the master list/key that prohibits releasing it to the investigator under any circumstances or until the individuals are no longer living. Investigators who wish to use this option must submit an appropriate plan with documentation of the agreement to OPHS with the IRB application. Consult with OPHS staff for additional guidance on this topic.

Another important consideration in evaluating risk will be the nature of the study. Studies that examine germline cells, which contain inherited material from eggs and sperm that are passed to offspring, represent the greatest amount of risk because they relate to the inherited potential of the individual, which can have direct implications for current and future generations as well as racial/ethnic groups. Studies that examine typical (somatic) cells in the human body (internal organs, hair, skin, eyes, bones, blood, and connective tissue) are generally considered to be lower risk because they should not have direct implications for current and future generations.

Informed Consent to Use Specimens for Research Purposes

Human subjects protection regulations apply to the use of human samples in research studies. Therefore, to be in compliance with federal regulations, informed consent should be obtained from the subject prior to using his or her samples for research purposes (see Section 9.2 on the General Requirements of Informed Consent).

There are several types of research involving specimens, and each has its own set of regulatory, ethical and practical aspects and features:

- Retrospective Specimen analyses – in which samples have already been obtained for either clinical (non-research) purposes, or through an IRB-approved research collection protocol. These samples would constitute an “existing” sample collection. Note that in some cases, a project may involve both existing and ongoing (prospective) samples.
- Prospective Sampling – in which samples are being collected through an existing IRB-approved protocol, or will be collected for clinical (non-research purposes)
- Specimen Repositories (also know as Tissue-Sample Banks) – which may have also have data (medical, behavioral, demographic, etc.) associated with specimens

Research Involving the Use of Existing Specimens (Retrospective Specimen Studies)

In these studies, the samples already exist, having been collected for non-research purposes (via clinical care) or through a previous IRB-approved study.

It is important to consider that patients may give their permission for their samples to be used for research purposes when they consent to a medical procedure, or when they are admitted to a hospital or treatment center. OPHS recommends that investigators review medical intake forms at the entity where the samples

were obtained prior to contacting OPHS for guidance on preparing their IRB application. OPHS staff will need to know this information before they can appropriately advise the investigator on how to proceed. Additionally, investigators will be required to submit a copy of the clinical document, such as a clinical consent form, indicating patient consent for their samples (and related data) to be used for research purposes. Again, a copy of these clinical consent documents should be submitted to OPHS along with the IRB application.

Waiver of Informed Consent

DHHS regulations permit the IRB to consider waiver of informed consent in research that involves samples for which informed consent was not obtained if the research meets the required criteria for Waiver of Informed Consent (see Section 9.7). The OPHS/IRB will evaluate the following when an investigator requests that informed consent be waived:

1. Wishes of the subject (personal autonomy);
2. The type of consent given for the tissue storage in the repository;
3. If the data associated with the sample will be secure and confidential after it is released to the researcher from the repository.

Additionally, HIPAA permits the use of unidentifiable samples collected prior to April 14, 2003 without informed consent in some situations (contact OPHS staff for guidance). Current FDA regulations do not permit any waivers of informed consent.

Investigators should submit the appropriate waiver form (see Appendix C) with their IRB application when requesting a waiver of informed consent. *Please Note:* To facilitate review, please make sure to initial, provide an appropriate explanation, and sign the form. Failure to complete the form appropriately may lead to a delay in the review/approval process for the IRB Application.

Research Involving the Prospective Collection of Specimens

Studies that involve the prospective collection of human samples will not be eligible for Exempt review. Therefore, investigators will need to submit an Expedited or Full Board IRB application to OPHS. Investigators should contact OPHS staff for guidance in determining the type of application that will be required when they are developing their protocol.

Per federal regulations, some research that involves samples may be eligible for Expedited review. This includes research that involves the collection of blood samples by finger stick, heel stick, ear stick, or venipuncture, and research that involves the prospective collection of biological specimens for research purposes by noninvasive means (refer to Section 5.13 for specific detail).

In prospective studies, the collection of the sample may be solely for the purpose of the specific research project. The collection of the sample is (or is part of) the research intervention, which will typically occur at a research study visit.

However, in many prospective studies that involve samples, the collection occurs at a clinic visit or hospital stay rather than a study visit. Researchers may request permission to analyze the sample that is collected during the medical visit for research purposes. Subjects may also be asked to provide an additional sample (for example, “an extra vial of blood” or an “extra swab”) at their clinic or hospital visit

for the research study. In these studies, clinicians and other medical personnel (such as physician assistants, nurses, and medical assistants) are often involved in the conduct of the research study by obtaining and transferring the sample to the investigator for analysis and storage.

A proper informed consent process will need to be in place for all prospective studies. The informed consent should clearly describe the process and procedures for the storage and future use of the human sample(s). The informed consent should also describe if identifiers linking the subject to the sample will be present, and if the subject can withdraw their sample from the study or repository in the future if they no longer wish to participate in the research (note that subjects whose samples will be unidentifiable will not be able to withdraw from the research in the future). All persons who are obtaining informed consent from subjects in prospective studies that involve samples should be listed as key personnel in the initial IRB application and protocol, or added using the "Application for Change in Study Personnel" form if they are added to the study after IRB approval. All key personnel are required to complete the appropriate educational training in the protection of human subjects, and submit a signed Conflict of Interest Form to OPHS if they are faculty, students, or employees of UNTHSC or UNT Health (see Section 8.2 for additional details on educational requirements).

Repositories

After collection, samples may be stored in specimen repositories or "tissue banks." The repository may be small or may be very large with thousands or millions of samples. OPHS and the IRB are concerned with the following three types of repositories:

1. Repositories of samples collected prospectively for a research study or possible future research study;
2. Repositories of clinical samples that were collected during medical procedures, to be used in the future for diagnostic and/or predictive purposes; and
3. Banks of clinical samples for which there is excess tissue/material (beyond which is needed for future medical diagnosis) that may be accessed for research purposes.

Repositories that include samples that will be used in research studies should have an appropriate IRB approved plan in place to regulate the collection, storage, and distribution of samples. IRB review and oversight will be required for all such repositories that reside at UNTHSC (see additional detail below).

Banks of clinical samples not intended for research may not be subject to federal regulations or IRB review unless required the repository is federally funded or if IRB review is required by the institution. UNTHSC currently does not require IRB approval for banks of clinical specimens that are not intended for research purposes. However, HIPAA regulations will apply to the clinical samples stored in these repositories. In all cases, it is important to avoid the regulatory problem created by collecting samples in a clinical care enterprise that are actually intended for research purposes. If there is any expectation that samples may be used for research purposes in the future, it is best to establish that assumption at the beginning, and create a research specimen repository in compliance with federal regulations. Consult with OPHS staff for guidance on this topic.

Establishing Repositories at UNTHSC for future research use

Investigators who wish to create a repository of human samples that will be used for future research purposes will need to obtain IRB approval prior to establishing the repository. These Principal

Investigators become “Repository Controllers” who establish and manage the collection, storage, access, and distribution of repository specimens. The IRB will review the operating procedures of the repository, including who will have access to the samples, coding of samples, and the process to ensure that future research projects are not conducted without prior IRB approval. Additionally, the IRB will consider ownership of the samples, privacy and confidentiality, process for withdrawing samples from the repository, plans for the transfer of samples to internal and external investigators, and oversight of future research involving the banked samples. The investigator may plan to use the banked samples for a variety of purposes. If so, this should be clearly described in the protocol synopsis.

Samples that will be prospectively obtained from subjects will require the informed consent of the subject before they can be placed in the repository. This consent should include the core elements described in the federal regulations at 45 CFR 46 (see Section 9.2). Additionally, it may be appropriate to provide an “opt in” and “opt out” option in the consent form that allows subjects to determine which types of entities/individuals may use their tissue for research (i.e. nonprofit, commercial, specific researcher) and for what purpose the samples may be used (i.e. cancer research, cardiovascular health research, gynecological research, etc). This is especially important for banked samples that will be used for a variety of research purposes. Existing samples that an investigator wishes to place in a repository may qualify for a Waiver of Informed Consent or they may require the consent of the subject (informed consent is described in the next section). Establishing a repository using donated and/or purchased samples is also discussed in greater detail later in this section.

It is important for investigators to remember that after the repository has been established, each individual research project that will utilize samples from the repository will require an individual IRB review and approval. Some of this research may qualify for Exempt review by OPHS. However, the individual(s) responsible for the oversight of the repository will need to ensure that access to the banked samples is only granted with IRB approval. Further, Repository Controllers (see above) should also be included as key personnel on the protocol to verify access and authorization for repository specimens and their associated data.

Additionally, in some circumstances, the IRB may require that a person whose sample is in the repository provide additional consent (i.e. be “re-consented”) to allow researchers to use their sample for their research. An example would be research that involves HIV testing of stored samples. This may involve re-contacting subjects to obtain their consent. Including an “opt in” and “opt out” clause in the consent form may reduce the need to re-contact subjects. Guidance on re-contacting subjects can be found on the OPHS website under “Guidance or How to Pages”/Designing Research Protocols” or by selecting the following link: <http://www.hsc.unt.edu/Sites/OPHS-IRB/Documents/Re-Contacting%20Guidance%20for%20Investigators.pdf>

Research using Existing Donated or Purchased Samples

Creating a Repository using Donated or Purchased Samples

Research studies at UNTHSC may involve the collection and analysis of existing samples and related health information donated by, or purchased from, an outside entity or individual. The investigator may wish to create a repository at UNTHSC that includes these donated samples and related health information. The related health information may be extensive in some situations (for example, an entire medical chart), and include a great deal of Protected Health Information (PHI). Investigators will be required to describe, in the protocol synopsis, to what extent the samples and related data will be de-identified before arriving at UNTHSC. Additionally, investigators should also describe, again, in the

protocol synopsis, the process in which identifiers will be “stripped” from the medical data. If the breadth of health information is extensive, the IRB will require that all identifiers be removed before the samples arrive at UNTHSC.

Ensuring Donated or Purchased Samples are Legally and Ethically Obtained

It is important that investigators ensure that the samples received from the outside entity were and continue to be legally and ethically obtained. Documentation describing how the samples were obtained should be submitted with the IRB application.. This may be demonstrated by obtaining a copy of IRB approval for the collection of samples from the outside entity. Please Note: A copy of the outside entity’s IRB approval should be submitted to OPHS with the UNTHSC IRB application.

Ownership of Samples

Investigators should describe, in the protocol synopsis, who will own the samples and related data after they arrive at UNTHSC, and indicate if the outside entity/individual will retain any ownership or access to the samples after they are transferred to UNTHSC.

Transfer of Samples and Related Data to other UNTHSC Researchers

An investigator serving as the Repository Controller may wish to allow other UNTHSC researchers to use samples stored in a repository for future research purposes. In this case, a section titled “Transfer of Specimens and Data to UNTHSC Researchers” should be included in the protocol synopsis. This section should describe the process for how specimens and data will be transferred to other investigators at UNTHSC. As mentioned earlier, an entirely new IRB application will be required before an investigator can access these samples or data for their individual research project.

Transfer of Samples and Related Data to Outside Researchers

An investigator may wish to transfer samples to an outside researcher for several reasons. The outside researcher may be involved in the analysis of the samples and related data for a current research project the investigator is conducting, or for a collaborative research project conducted by both UNTHSC and an outside entity. Additionally, an investigator may wish to allow an outside researcher to use samples stored in a repository for a future research project that does not involve UNTHSC.

In all cases, an appropriate set of procedures will need to be in place to protect the subject’s confidentiality during this transfer. Investigators are encouraged to consider such future arrangements and to establish these procedures within the initial protocol application. However, there may be situations when it is necessary to modify an existing IRB approved protocol to include this option. The protocol should include a section titled “Transfer of Specimens and Data to Non UNTHSC Researchers” that describes a detailed plan for the transfer of samples to outside researchers. To protect subject confidentiality, the protocol should describe how the samples and data will be labeled when they are transferred, and the process for “stripping” all identifiers from the data before they leave UNTHSC. The protocol should also list the outside researchers by name, and describe who will own the samples after they are received by the outside investigator if this information is available. OPHS understands that an investigator may not be able to name a specific outside researcher during the initial IRB application process or request for modification to the protocol, however would like to include this option should there be a future need to transfer samples. It is appropriate to incorporate this option into the protocol. As mentioned above, the protocol should include a section titled “Transfer of Specimens and Data to Non

UNTHSC Researchers” that describes an appropriate plan including how samples will be labeled and stripped of identifiers prior to transfer. Once the Principal Investigator (PI) has identified the outside entity who will receive and analyze the specimens, that PI is required to submit a request for approval to OPHS. This memorandum should name the outside entity, describe what the outside entity will do with the samples, describe who will own the samples after they are received by the outside entity, and how the samples and accompanying data will be securely maintained. The investigator should not send the samples and/or related data to the outside entity until they have received notice of approval in writing from the OPHS/IRB.

Subjects should be advised during the initial informed consent process that their samples and/or related data may be sent to an outside entity that is approved by UNTHSC for research purposes. Only subjects who consent to the transfer of specimens should have their samples and/or related data sent to outside researchers. In some cases, it may be necessary to re-contact and re-consent subjects who were advised that their samples and/or related data would not be transferred to outside researchers during the initial informed consent process. Investigators are encouraged to contact OPHS staff for guidance in this area. This will not be applicable for studies that qualify for a Waiver of Informed Consent.

Research Using Samples from Deceased Persons

Federal regulatory definitions of human subjects does not include deceased persons. Therefore, the use of samples obtained during an autopsy or the use of samples originally collected from a living individual who is now deceased is not considered research with human subjects. However, in most cases, other federal and state regulations may apply including HIPAA regulations. Investigators are encouraged to contact OPHS staff prior to initiating this type of research to ensure that appropriate HIPAA and/or IRB compliance is followed.