

SCI Protocol #: **SCI 08-002**

SCRIHS Protocol #: **08-112**

TITLE: **Simmons Cancer Institute at
Southern Illinois University School of Medicine
Tissue Bank Protocol**

Coordinating Center: **Simmons Cancer Institute
SIU School of Medicine**

Tissue Bank Director: Morris Cooper, Ph.D.
Professor and Chair
***Committee Chair** Medical Microbiology and Immunology\
SIU School of Medicine
801 N. Rutledge Street
P.O. Box 19626
Springfield, IL 62794-9626
Telephone (217) 545-8462
mcooper@siumed.edu

Committee Members: **Elizabeth Peralta, M.D.
James Malone, M.D.
Randolph Elble, Ph.D.
John Godwin, M.D., M.S.
Kathy Robinson, Ph.D.**

K. Thomas Robbins, M.D. (ex officio)

Tissue Bank Technician: **Tissue Bank Technician
911 N. Rutledge
Room 337
Springfield, IL 62794-9677
Phone (217) 545-9708
Fax (217) 545-1398**

IND Number: **Not Applicable**

Protocol History

Version #: 8.0

Version Date: 9-30-2010

| Version Number | Amendment Date | Reason for Amendment |
|----------------|----------------|--|
| 1.0 | none | original |
| 2.0 | 11-19-2008 | Requested Revisions from the IRB |
| 3.0 | 12-10-2008 | Requested Revisions from the IRB |
| 4.0 | 1-12-09 | Requested Revisions from the IRB |
| 5.0 | 9-23-2009 | Clarification of information to be released with specimens |
| 6.0 | 11-24-2009 | Transfer PI to Kathy Robinson and Remove Dr. Mo and Qing Yang from documents |
| 7.0 | 5-13-2010 | Update name of SCCI to SCI, clarifications |
| 8.0 | 9-30-2010 | Transfer PI and directorship to Morris Cooper; formatting & clarifications |
| | | |

Introduction

Human tissue and bodily fluids are often required in medical research to verify and expand information acquired from animal models and cell lines. Unfortunately, without the collection of human biospecimens, these experiments are not possible. Surgical procedures to remove tumors or to correct a medical problem often results in tissue or bodily fluid collection for various laboratory or pathological procedures. However, excess tissue or specimens not needed in normal medical practice are often destroyed. Utilization of excess tissue and biospecimens allows scientists to study a variety of disease mechanisms in a human model, leading to the advancement of science. For this purpose, tissue banks have been organized around the world to collect, process, and store operative and autopsy specimens for future research endeavors.

Purpose/Objective

The purpose of the Simmons Cancer Institute Tissue Bank is to serve as a resource for scientists needing human biological specimens (see definition below) through the collection and storage of tissue and blood. In addition to the biospecimen collection and storage, the Tissue Bank's purpose is to maintain clinical and pathological information pertaining to the specimens. Additional clinical information (beyond what is outlined for release with all specimens), if requested, may be obtained through additional sources. A separate IRB approval or exemption will be required for information released from the SCI patient registry or the patients' charts, including outcomes of treatment. The Clinical Research Office will be the "broker" for accessing the code to identifiers related to the specimens. The Tissue Bank will support a wide array of current and future research which requires human biospecimens and may lead to the further understanding of the mechanisms of cause, prevention, and cure of human disease states. Donated tissue, blood, and/or other bodily fluids may assist in answering research questions regardless of the donor's health state at the time of collection.

Definition: Human biological specimens.

A human biological specimen is any material derived from a human subject—such as blood, urine, tissues, organs, hair, nail clippings, or any other cells or fluids—whether collected for research purposes or as residual specimens from diagnostic, therapeutic, or surgical procedures. The SCI Tissue Bank will only collect blood and tissue unless specimen requests indicate other biospecimen types may be needed. The collection of additional types of specimens will be reviewed at such a time and the protocol amended if applicable.

Organizational Structure

The internal organization of the Tissue Bank will include a Director, appointed by the Cancer Center Director, a Tissue Bank Technician, a Tissue Bank Committee, and the Cancer Center Clinical Research Office. The Tissue Bank Director will be responsible for the maintenance and integrity of the tissue and information collected for the Bank's biospecimen database. The Director will also provide direction and supervision to the Tissue Bank Technician, as well as

oversee the collection, storage, and processing of the donated human biological specimens. The Tissue Bank Director is responsible for the integrity of the entire process of collection and storage and reports to the Cancer Center Director. The Tissue Bank Technician will assist in the direct collection, transport, storage, and processing of specimens for the bank. The Clinical Research Office of the Simmons Cancer Institute is responsible for the storage of the original informed consent documents, HIPAA Authorization, and associated Collection and Tissue Release Forms.

The Clinical Research Office will also maintain a separate database of donor identifiers and related health information that is linked to de-identified specimen information maintained in the Tissue Bank database. The Clinical Research Office of the Simmons Cancer Institute will conduct regular audits (not less than once per year) of the tissue bank to assure the integrity of the data and program and will supervise the initial training and annual proficiency reviews of the Tissue Bank Technician and all personnel involved in the consent process (i.e., designated clinic nurses –see below). The Simmons Tissue Bank Committee will also be responsible for the receipt and processing of requests from IRB approved studies for any additional information beyond age, gender and pathological data (i.e. type of cancer) of the tissue. The Clinical Research Office may be approached by an individual investigator in the collection of such data once IRB approved (e.g. chart review).

A Tissue Bank Committee, comprised of basic and clinical scientists, will be appointed by the Simmons Cancer Institute Director and its Executive Committee to advise the Tissue Bank Director, review processes on a regular basis, address internal audit reports, assure quality, review initial and annual proficiency training reports, respond to external requests, review and approve the annual protocol report, and approve all requests for tissue distribution. The Tissue bank Committee membership will consist of permanent members who are the Tissue Bank Director, the Associate Director for Clinical Research or designee, a representative from the Clinical Research Office and the Cancer Center Director (ex officio). Two or three additional members from the SCI will serve renewable two year terms. The Tissue Bank Committee will establish guidelines which are achievable and in compliance with all applicable and regulatory requirements. Standard operating procedures (SOPs) will be developed and approved by the committee to ensure that methods are in place for the appropriate collection, processing, storage, and distribution of stored samples.

The Tissue Bank Committee will meet regularly and as needed for the review and approval of all requests for removal/and or distribution of stored samples. The Committee is responsible for the assurance that the biological specimen distribution is to an authorized agent, and that the process is in compliance with all regulatory requirements.

General Procedures

Consenting of Donors

Human biological specimens will be collected from eligible donors. Eligible donors include

patients scheduled to undergo a therapeutic or diagnostic procedure which requires the collection of tissue and blood. Designated clinic staff will work closely with attending physicians/surgeons and nursing staff to identify eligible donors. Potential donors may also be identified through review of clinic or surgery schedules for donors who meet eligibility criteria. The primary focus of donors will be those patients seen by the Simmons Cancer Care Teams and who have a malignant tumor. However, the collection of “normal” tissue by patients undergoing elective procedures is also very important. The surgeons will make the judgment as to who should be approached from their clinics. The Tissue Bank realizes that patients may be overburdened at this time and may not be a good donor candidate at that moment.

Patients of all ages may be asked to donate tissue; however, the focus will be on adults. All donors under the age of 18 will have a parent or legally authorized representative sign the consent and the donor will be asked for assent if of adequate age to understand.

Eligible donors will only be approached if authorized by the donor’s attending physician/surgeon. The attending physician/surgeon will introduce the purpose of the Tissue Bank to the donor before he/she is approached for the informed consent process. Designated clinic nurses (see definition below) will describe the purpose and intent of the Tissue Bank, the donation procedure, risks to the donor, voluntary nature of the tissue/ biospecimen donation, and answer any questions the subject may have before offering the written consent to the subject for consideration. In most cases the donor will have time to review and discuss the donation process with family or support individuals.

Definition: Designated clinic nurses are SIU employees and/ or members of SCI staff and will undergo specific training in consent and Tissue Bank procedures under the supervision of the SCI Clinical Trials Office. Designated nurses must also complete the required IRB training prior to speaking with donors about this program.

Physician members of SIU Physicians and Surgeons which agree to participate and have completed their IRB training will sign the consents. Original signed consent forms will be stored in the Clinical Research Office with a copy provided to the donor, and additional copies placed in the donor’s medical charts at the hospital and SIU Clinics by the designated clinic nurses.

Leftover Routine Care Specimens

During routine care, a surgical or therapeutic procedure may be necessary as part of the diagnosis or treatment of a specific disease. It is common for tissue to be leftover after the necessary tests have been performed. The Tissue Bank will consent eligible donors to collect this leftover tissue since it may be useful in future research. No additional tissue is needed and will not affect the outcome of the tests or procedures.

At the same time, donors will be asked to donate about 4 teaspoons of blood. In order to minimize discomfort, blood will be obtained during a blood test needed for diagnosis or treatment purposes or when an intravenous line needs to be placed as part of usual care.

Leftover Research Specimens

Leftover research specimens are from eligible donors who have been approached and signed an informed consent for a protocol other than the SCI Tissue Bank. Inclusion of these biological specimens in the Tissue Bank requires a special optional tissue banking consent to be attached to the original research consent. The specimens are the remaining unused portions that were collected for research specifically related to the original research protocol. These leftover research specimens will undergo the same process of storage with de-identified information in the biospecimen database, while protected health information is kept in the SCI Clinical Trials database.

Additional Clinical Information

Additional identifiable information from the donor's medical record, including identifiable information about personal and family histories of disease, lifestyle factors, physical examinations, diagnostic tests, specific clinical interventions, hospital course, and follow-up data will be available if approved or exempt through a separate IRB review. The clinical research office may assist with this collection of information if requested. The information will be obtained from the SCI patient registry and possibly chart review. The additional identifiable information request including identifiers per the Privacy Act (18 identifiers) must be accompanied by documented proof of IRB review of the research protocol. All information released will be de-identified prior to release, unless otherwise specified and approved by the IRB. Additional information which would not allow the re-identification of a donor (through a single variable or the combination of variables) will be provided as requested to investigators, such as previous treatments and family history (if it is not usable for re-identification).

Data Management

The Tissue Bank Technician will assign a unique identification code to each specimen to be included in the Bank. Samples will be stored under appropriate conditions (liquid nitrogen, -80° C freezer, etc.) located in a secure room in the 911 N. Rutledge Laboratory Facilities. Limited donor information (age, gender, and tissue pathology, and general treatments the donor may have been exposed to [radiation, surgery, chemotherapy, combination]) will be entered into the Tissue Bank biospecimen database, along with the identification code. This biospecimen database is password protected, located on a secure computer located in the Tissue Bank Collection and Processing Room. Data are backed-up to network drives accessible only to SCI personnel.

The CREDIT software system (only accessible by the clinical research staff) will be used to track all consented participants and act as a key in which the donor name and the unique tissue identification code will be matched, enabling the linkage of the tissue with personal health information. All clinical information relevant to the donor and their care will be stored in the Simmons Cancer Patient Registry or remain within the donor medical chart. Clinical Research Staff may access the donor's information (computer records, medical records) to update the CREDIT software or Simmons Cancer Institute Patient Registry as information becomes

available. Updated information may include relevant clinical follow-up information and treatment information. Both the patient registry and CREDIT system are password protected and will be controlled by the Clinical Research Office.

Tissue Allocation

The Tissue Bank Committee will be responsible for developing appropriate request forms for the request of biospecimens, as well as the distribution priorities. Investigators interested in obtaining biospecimens from the bank will be required to submit an application to the Tissue Bank Committee. Approved applications will trigger the release of de-identified specimens and clinical information (as requested and approved by the IRB) to the investigator. Upon application approval, the investigator, the Tissue Bank Director, Tissue Bank Technician, and the Clinical Research Office Data Manager will enter into a Tissue and Data Use Agreement (see attached) prohibiting the release of donor health identifiers (PHI). The Tissue Bank Request SOP describes in detail the process for review and release of biospecimens.

As investigators will not have access to PHI, and both conditions of the October 16, 2008 OHRP Guidance on Research Involving Coded Private Information or Biological Specimens (See Appendix A; page 3, guidance 1 & 2) are met, research involving the collected specimens is NOT considered to involve human subjects under the HHS Protection of Human Subjects Regulations (45 CFR Part 46.102(f)).

An exception to the above practice may occur in the event an IRB approval is granted for the release of, or access to, identifiers to the investigator through a separately approved IRB protocol. Donors will be given the option to allow an investigator to contact them in the future.

OPERATIONAL PROCEDURES FOR COLLECTION AND STORAGE OF TISSUES

The following instructions explain how human biospecimens will be identified, procured, and processed for the SCI tissue bank. Detailed Standard Operating Procedures (SOPs) will provide additional information.

Procedures for Obtaining Tissues from Surgery

Tissues obtained through surgery include those tissues which are routinely resected for diagnostic or therapeutic purposes.

A. Clinic staff which have agreed to participate in the tissue collection process will identify potential donor participants. Any patient who is scheduled for surgery is eligible though adults with malignant tumors will be the primary focus.

B. If the appropriate and valid donor consent has been obtained by designated clinic nurses, the tissue bank technician will notify the appropriate personnel at the hospital (or clinic in instances

of non-surgical collection of specimen) of the impending collection where the surgical procedure is to take place. This will usually include surgical pathology and the surgery scheduling office.

Memorial Medical Center: One day prior to the scheduled surgery, the surgery scheduling office will be called and notified of a case of tissue banking. The technician will ask that the surgical staff be informed of the tissue collection and ask that 2 tubes of blood (one for whole blood and one for serum) be collected from the donor while in surgery. The technician will also call the general surgery scheduling office the day of the surgical procedure and ask to speak with the OR staff to remind them of the collection of specimens. Surgical Pathology will be notified of the collection the day of the procedure, as well.

St. John's Hospital: One day prior to the scheduled surgery, the surgery scheduling office will be called and notified of a case of tissue banking. The technician will ask that a note be added to the case for Anesthesia and the OR staff of specimen collection. The note to Anesthesia will consist of a request for 2 tubes of blood to be drawn from the donor while undergoing surgery (one for whole blood and one for serum). The day of the surgical procedure both the surgical staff and surgical pathology will be called and reminded of the specimen collection.

Clinics: To be arranged on an individual basis with the tissue bank technician.

All hospitals and clinics will be provided with the tissue bank pager contact number for notification that specimens are available in pathology for pick up by the tissue bank technician. Surgical pathology will be instructed to not place the tissue in formalin.

The tissue bank technician will immediately pick up the specimen(s) from surgical pathology. A liquid nitrogen Dewar flask will be brought for tissue transport as well as all needed supplies. The technician will provide the surgical pathologist with weigh boats marked NORMAL and TUMOR and the pathologist will provide any excess available tissue which fits the description of normal or tumor. The surgical pathologist will have already completed a gross inspection and processed any clinical samples needed for diagnostic purposes prior to release to the tissue bank technician. The tissue bank technician will follow-up with the processing and storage of the collected samples.

Procedures for Obtaining Blood Samples

The donor will also be asked to provide 2-4 teaspoons of blood (2, 5-10ml tubes). In order to minimize the distress to the donor, all blood samples will be obtained during a blood test needed for diagnosis or treatment or when an intravenous line is required as standard of care. In the event a donor is undergoing a surgical procedure, the tissue will be collected on the day of surgery. The tissue bank blood specimens will be collected in 2 tubes, one appropriate for whole blood, and one appropriate for serum collection. The tissue bank technician will collect and process the specimens at the time of tissue collection. If the donor is not undergoing a surgical procedure, the technician will make special arrangements to pick up the blood at the time of the donor's laboratory procedures.

Procedures for Processing of Specimens

Once the tissue bank technician has returned to the processing laboratory with a specimen, a special coded specimen identifier will be assigned for each sample. The specimen identifier along with associated data will be entered into the biospecimen database as well as a New Specimen Form. Labels will be provided for specimen identification.

All specimens to be frozen will be done so within 60 minutes of resection.

SOPs for the processing of specimens will be finalized by the Tissue Bank Committee prior to the initiation of the new Tissue Bank Protocol.

Ownership of the Specimens

All specimens collected under protocol SCI 08-002 are the property of the Simmons Cancer Institute. All specimens will remain in storage indefinitely until use by an Investigator. In the event the Simmons Cancer Institute would withdraw the active collection and release of specimens from the bank the Tissue Bank Committee will make a recommendation to the Simmons Cancer Institute Executive Committee on what should be done with the remaining tissue in the bank.

Request for Release of Biospecimens

Investigators requesting specimens from the bank must file an application for release and sign a Use Agreement for every request. The Tissue Bank Technician, Tissue Bank Director, and Tissue Bank Committee will all be involved in the process of application and approval for release as outlined in the SOP for release of specimens. If the Tissue Bank Director or another Tissue Bank Committee member is requesting the release of a specimen, that individual will remove himself/ herself from the process of application and approval and act only in the role of investigator. The committee will appoint an appropriate designee from the committee to act in the director's place, when the director is the individual making the request for a specimen.

Information to be released with specimens includes age, gender, and tissue pathology. Tissue pathology includes any and all information on the surgical pathology report excluding direct identifiers such as dates of service, donor name, accession numbers, and medical record numbers. Examples of information to be released include tumor characteristics, additional staining or biomarker reports, microscopic diagnosis, clinical diagnosis, description of the surgical margins and gross description of the surgical specimen. General prior treatment information such as radiation, surgery, chemotherapy or biologic therapy may be given upon request. Specific identifying information (based on the Privacy Act 18 specific identifiers) will not be given out without separate IRB review.

Quality Control

Scientists often devote extensive time and resources into experiments that utilize tissue bank biospecimens. The quality, therefore, of each specimen must be of highest quality possible. Variations in quality may produce varying results in experiments. For this reason, quality control of the donated tissue and samples is extremely important. Each donated tissue must be reviewed by a pathologist and various parameters noted.

Occasionally, 'tumor' specimens collected may contain inadequate representations of viable tumor cells or mixtures of both malignant and hyperplastic characteristics which cannot be separated. Likewise, tissue collected as normal may show ischemic or inflammatory characteristics and even contain unsuspected involvement by tumor.

Some of these characteristics would not necessarily exclude a specimen from being reserved for specific studies. Involvement by tumor, however, would definitely exclude a specimen from the 'normal tissue' collection and the severity of the other characteristics may also result in the rejection of the specimen.

Laboratory Safety Related to the Collection and Processing of Tissue

The collection, processing, and distribution procedures of the Simmons Tissue Bank will be conducted in a manner and environment as safe as possible. These safety practices also include the transport, acceptance and use of the biospecimens. Therefore, each laboratory/ investigator must agree to instruct all personnel involved in the use of the biospecimens on the safety of such exposures. OSHA requires this of many laboratories, as well.

To assist in this education, various references and guidelines dedicated to laboratory safety, including those from governmental agencies, are provided. Additional information may also be obtained from regulatory agencies and organizations. These include:

Occupational Safety and Health Administration (OSHA)
Centers for Disease Control (CDC)
College of American Pathologists (CAP)
The National Research Council (NRC)
The National Committee for Clinical Laboratory Standards (NCCLS)

OSHA Requirements

"Occupational Exposure to Blood Borne Pathogens: Final Rule", Federal Register P64175-64182, December 6, 1991.

Federal Regulation 29CFR Part 1910.1030 went into effect March of 1992.

This section of the Code of Federal Regulations "applies to all occupational exposure to blood or other potentially infectious materials". Essentially, this rule pertains to those situations in which an employee, as part of his or her duties, has reason to anticipate skin, eye, mucous membrane, or parenteral (e.g., piercing of skin or mucous membrane) exposure to human blood containing microorganisms which may cause disease in humans. Employee protection against the hepatitis viruses and human immunodeficiency viruses are the basis of these regulations; however, these

regulations also apply to individuals working in histology and tissue process laboratories, as well, and employee protection from a wide range of blood borne pathogens or otherwise infectious materials to which they may be exposed.

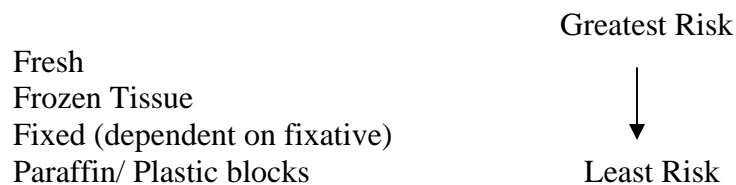
The elimination and minimization of employee exposure to infectious agents through controlled work practices and equipment is the primary goal of the regulation. Employers are required to establish a written plan to limit the exposure of employees to infectious material. The risks associated with exposure to such infectious agents involved with various job tasks and methods to reduce the likelihood of exposure are identified in the plan. Employees must be informed of these risks. The employer is responsible for developing and instituting the methods with the intention of limiting the exposure of the employee to the infectious agents. The OSHA regulations provide guidelines on work practices and equipment that lessen the chance of exposure. All personnel involved in the processing or handling of tissue should read, understand, and follow this document.

29CFR 1910.1030 also requires the establishment of an annual training program for all employees and maintenance of training records for a minimum of 3 years. Individuals providing the training must be knowledgeable in the subject and provide the training in a language and education level appropriate to the employee. The regulations provide standards to which the content must meet, including information on epidemiology, symptoms and mode of transmission of blood borne disease, employer's exposure control plan, selection and use of personal protective equipment, signs and labels used to identify infectious material, methods to reduce the chances of personnel exposure, procedures and follow-up in the event of exposure, and an opportunity to ask questions of the instructor.

Labeling of work areas, contaminated equipment, tissue storage and transport containers, regulated waste, and contaminated storage containers with biohazard signs are required. Laboratories supplying tissue to investigators must be careful to comply with these requirements. All tissue transported out of the tissue bank will be in a receptacle properly marked with a biohazard symbol and written instructions which state the container should remain closed unless these guidelines have been read and understood.

Biohazards in relation to Tissue Processing

Individuals that practice human tissue collection and processing have varying biohazards based upon the state of the employee's immune system (normal vs. compromised). The diagram below demonstrates the association between tissue state and risk.



Fresh animal or human tissue pose the greatest risk with frozen tissue being slightly less infectious, as some pathogens may sustain viability through freeze-thaw cycles. Fixed tissues, depending on the fixative used and the pathogenic micro-organism, may vary greatly in risk of infection. The least risk for infection is associated with paraffin or plastic embedded tissue. However, some pathogens may remain infectious even when processed as paraffin embedded tissue. These include: tuberculosis mycobacterium, Creutzfeld-Jakob disease and related animal diseases (scrapie, mink encephalopathic virus, deer/ elk wasting disease, bovine spongiform encephalopathy). Phenol and bleach (sodium hypochlorite) are the most effective agents for inactivating prions of Creutzfeld-Jakob disease. Instances of such pathogens, however, are rare for the populations seen at SIU.

Hepatitis Band C viruses pose the most danger to laboratory workers processing human tissue. The danger lies in the fact that these viruses contaminate many tissue types and is highly infective of non-intact skin. Although Creutzfeld-Jakob disease and HIV represent significant dangers to the laboratory professional, Hepatitis B infections result in higher numbers of associated deaths simply due to the fact that a greater number of individuals, through personal and professional lives, are exposed to the pathogen. Danger of HIV infection is becoming an increasing concern as the incidence of HIV infection rises. The greatest danger may come from tissues positive for more than one pathogen. HIV, hepatitis B, C and hepatitis delta antigen may be found within the same patient as the modes of transmittal (sexual contact and IV drug abuse) are the same. HIV patients with AIDS pose an additional danger as increasing numbers of infections from mycobacterium tuberculosis and atypical mycobacterium are discovered, which may also be transmitted to individuals with normal immune systems.

The guidelines represented here are only that—GUIDELINES. All persons involved in the handling or processing of human tissue should be aware that information on the dangers of handling tissue and potential pathogens is ever evolving. Tissue Bank personnel must keep themselves informed of the potential hazards represented by Hepatitis viruses, HIV, AIDS, Creutzfeld-Jakob Disease, and other infectious pathogens. Unidentified pathogens may also pose a risk to laboratory personnel.

LABORATORY PERSONNEL INVOLVED WITH THE HANDLING OF HUMAN TISSUE WILL ALWAYS BE AT RISK FOR INFECTION FROM PATHOGENIC ORGANISMS PRESENT IN COLLECTED HUMAN BIOSPECIMENS, IDENTIFIED OR NOT. THE GUIDELINES AND INSTRUCTIONS HERE ARE NOT GUARANTEED TO BE ADEQUATE FOR THE PROTECTION OF INVESTIGATORS AND LABORATORY PERSONNEL FROM INFECTIOUS AGENTS. THE RESPONSIBILITY OF LABORATORY SAFETY IS THAT OF THE LABORATORY ADMINISTRATORS, AS WELL AS ALL PERSONNEL WORKING WITHIN THE LABORATORY.

Laboratory administrators and personnel are highly encouraged to remain current on safety guidelines and information for the protection of clinical laboratory workers issued by federal, state, and private agencies, including the CDC, OSHA, CAP, and NCCLS. Laboratory workers are responsible for utilizing the information available to them and making the protection of

themselves and their co-workers from unintentional exposure to infectious agents a priority.

REFERENCES

Basilar J.C., Gaylor D., Grizzle W.E., et al. Monitoring human tissues for toxic substances. National Academy Press. Washington, D.C., 1991.

DeMarinis A.J. Best practices in human tissue repositories. *Research Practitioner*, 7(1): 12-20, 2006.

Department of Health and Human Services, National Institutes of Health, First-generation of guideline for NCI-supported biorepositories, *Federal Register*, 71 (82). April 28, 2006.

Eltoum I., Frost A.R., Siegal G.P. Laser capture microdissection: past, present, and future. *Advances in Anatomic Pathology* 9: 316-22, 2002.

Frost A.R., Eltoum I., Siegal G.P. Laser capture microdissection. In: *Protocol in Molecular Biology*. John Wiley and Sons, Inc. 25A.1.1-25A.1.24, 2001.

Grizzle W.E., Woodruff, K.H. Trainer T.D. The pathologist's role in the use of human tissues in research-legal, ethical, and other issues. *Arch Pathol Lab Med* 120: 909-912, 1996.

Grizzle W.E., et al. College of American Pathologists position paper—Uses of human tissue in research, quality control and education. Ad Hoc Committee on Stored Tissues/ Genetic Testing, 1997.

Grizzle W.E., et al. Providing human tissue for research : How to establish a program. *Arch Pathol Lab Med* 122: 1065-1076, 1998.

McGuire A.L., Gibbs R.A. No Longer de-identified. *Science*, 312: 370-371, 2006.

<http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.htm> OHRP Guidance on Research Involving Coded Private Information or Biological Specimens, August 10, 2004.

<http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.htm> OHRP Guidance on Research Involving Coded Private Information or Biological Specimens, October 16, 2008.

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

APPENDIX A

Office for Human Research Protections (OHRP)

Department of Health and Human Services

Guidance on Research Involving Coded Private Information or Biological Specimens

NOTE: THIS GUIDANCE REPLACES OHRP'S AUGUST 10, 2004 GUIDANCE ENTITLED "GUIDANCE ON RESEARCH INVOLVING CODED PRIVATE INFORMATION OR BIOLOGICAL SPECIMENS." [CLICK HERE](#) FOR THE AUGUST 10, 2004 GUIDANCE. THIS GUIDANCE HAS BEEN UPDATED TO BE CONSISTENT WITH THE CONTENT OF OHRP'S OCTOBER 16, 2008 "GUIDANCE ON ENGAGEMENT OF INSTITUTIONS IN HUMAN SUBJECTS RESEARCH."

This guidance represents OHRP's current thinking on this topic and should be viewed as recommendations unless specific regulatory requirements are cited. The use of the word *must* in OHRP guidance means that something is required under HHS regulations at 45 CFR part 46. The use of the word *should* in OHRP guidance means that something is recommended or suggested, but not required. An institution may use an alternative approach if the approach satisfies the requirements of the HHS regulations at 45 CFR part 46. OHRP is available to discuss alternative approaches at 240-453-6900 or 866-447-4777.

Date: October 16, 2008

Scope: This document applies to research involving coded private information or human biological specimens (hereafter referred to as "specimens") that is conducted or supported by HHS. This document does the following:

(1) Provides guidance as to when research involving coded private information or specimens is or is not research involving human subjects, as defined under HHS regulations for the protection of human research subjects (45 CFR part 46).

(2) Reaffirms OHRP policy (see OHRP guidance on *repository activities* <http://www.hhs.gov/ohrp/humansubjects/guidance/reposit.htm> and *research on human embryonic stem cells* <http://www.hhs.gov/ohrp/humansubjects/guidance/stemcell.pdf>) that, under

certain limited conditions, research involving **only** coded private information or specimens is not human subjects research.

(3) Clarifies the distinction between (a) research involving coded private information or specimens that does not involve human subjects and (b) human subjects research that is exempt from the requirements of the HHS regulations.

(4) References pertinent requirements of the HIPAA Privacy Rule that may be applicable to research involving coded private information or specimens.

NOTE: Some HHS conducted or supported research involving coded private information or specimens may be subject to Food and Drug Administration (FDA) regulations. The FDA regulatory definitions of human subject (21 CFR 50.3(g), 21 CFR 56.102(e)) and subject (21 CFR 312.3(b), 21 CFR 812.3(p)) differ from the definition of human subject under HHS regulations at 45 CFR 46.102(f). This guidance document does not apply to research regulated by FDA that involves coded private information or specimens. Anyone needing guidance on such FDA-regulated research should contact the FDA.

Target Audience: Institutional review boards (IRBs), investigators, and funding agencies that may be responsible for review or oversight of human subjects research conducted or supported by HHS.

Background:

HHS regulations define *research* at 45 CFR 46.102(d) as follows:

Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

HHS regulations define *human subject* at 45 CFR 46.102(f) as follows:

Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains

- (1) data through intervention or interaction with the individual, or
- (2) identifiable private information.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which

the individual can reasonably expect will not be made public (for example, a medical record). Private information must be **individually identifiable** (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects (bolding added for emphasis).

For purposes of this document, *coded* means that:

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

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

OHRP considers the term *investigator* to include anyone involved in conducting the research. OHRP does not consider the act of solely providing coded private information or specimens (for example, by a tissue repository) to constitute involvement in the conduct of the research. Note that if the individuals who provide coded information or specimens collaborate on other activities related to the conduct of this research with the investigators who receive such information or specimens, then OHRP would consider such additional activities to constitute involvement in the conduct of the research. Examples of such additional activities include, but are not limited to: (1) the study, interpretation, or analysis of the data resulting from the coded information or specimens; and (2) authorship of presentations or manuscripts related to the research.

Guidance:

Under the definition of human subject at 45 CFR 46.102(f), *obtaining* identifiable private information or identifiable specimens for research purposes constitutes human subjects research. *Obtaining* identifiable private information or identifiable specimens includes, but is not limited to:

(1) using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that have been provided to investigators from any source; and

(2) using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that were already in the possession of the investigator.

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

Conversely, OHRP considers private information or specimens not to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or

indirectly through coding systems. For example, OHRP does not consider research involving **only** coded private information or specimens to involve human subjects as defined under 45 CFR 46.102(f) if the following conditions are both met:

- (1) the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and
- (2) the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:
 - (a) the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased (note that the HHS regulations do not require the IRB to review and approve this agreement);
 - (b) there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or
 - (c) there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

This guidance applies to existing private information and specimens, as well as to private information and specimens to be collected in the future for purposes other than the currently proposed research. The following are examples of private information or specimens that will be collected in the future for purposes other than the currently proposed research: (1) medical records; and (2) ongoing collection of specimens for a tissue repository.

In some cases an investigator who obtains coded private information or specimens about living individuals under one of the conditions cited in 2(a)-(c) above may (1) unexpectedly learn the identity of one or more living individuals, or (2) for previously unforeseen reasons now believe that it is important to identify the individual(s). If, as a result, the investigator knows, or may be able to readily ascertain, the identity of the individuals to whom the previously obtained private information or specimens pertain, then the research activity now would involve human subjects under the HHS regulations. Unless this human subjects research is determined to be exempt under HHS regulations at 45 CFR 46.101(b), IRB review of the research would be required. Informed consent of the subjects also would be required unless the IRB approved a waiver of informed consent under HHS regulations at 45 CFR part 46.116(c) or (d).

Who Should Determine Whether Human Subjects are Involved in Research

OHRP recommends that institutions have policies in place that designate the individual or entity authorized to determine whether research involving coded private information or specimens constitutes human subjects research. The person(s) authorized to make the determination should be knowledgeable about the human subject protection regulations. In addition, the institution should ensure the appropriate communication of such a policy to all investigators. OHRP recommends that investigators not be given the authority to make an independent determination that research involving coded private information or specimens does not involve human subjects.

Research not Involving Human Subjects Versus Exempt Human Subjects Research

OHRP is aware that questions often are raised regarding the distinction between research involving private information or specimens that does not involve human subjects (as above) and human subjects research that is exempt from the requirements of HHS regulations at 45 CFR part 46. This distinction can be made easier by always using the following sequential assessment when evaluating a particular activity conducted or supported by HHS:

(1) Does the activity involve *research*? If yes, proceed to question (2). If no, 45 CFR part 46 does not apply to the activity.

(2) Does the activity involve *human subjects*? If yes, proceed to question (3). If no, 45 CFR part 46 does not apply to the activity.

In analyzing a particular activity under the second question, it is important to focus on what is being **obtained** by the investigators. If the investigators are not obtaining either data through intervention or interaction with living individuals, or identifiable private information, then the research activity does not involve human subjects. Therefore, no assessment of the research activity using the third question below regarding exemptions is required because the exemptions provided for under 45 CFR 46.101(b) apply only to research involving human subjects.

(3) Is the activity exempt under HHS regulations at 45 CFR 46.101(b)? If yes, 45 CFR part 46 does not apply. If no, 45 CFR part 46 does apply.

With respect to research involving private information and specimens, the exemption that is most frequently relevant is the exemption under HHS regulations at 45 CFR 46.101(b)(4):

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

Having determined under the second question above that a research activity involves human subjects because the investigators are obtaining identifiable private information or specimens, assessment under the exemption at 45 CFR 46.101(b)(4) focuses, in part, on: (1) whether the data or specimens are **existing** at the time the research is proposed to an institutional official or IRB for a determination of whether the research is exempt, and (2) how the data or information is **recorded** by the investigators. This exemption would not apply if the investigators, having obtained identifiable private information or specimens from existing records or specimens, record the data or information in a coded manner, since the code would enable subjects to be identified through identifiers linked to the subjects.

To demonstrate how the determination of whether a research study is human subjects research differs from the determination of whether a human subjects research study is exempt under 45 CFR 46.101(b)(4), consider the following examples, in which an investigator obtains health

information of living patients who were treated for arthritis with either Drug A or Drug B. The investigator obtains this information in order to evaluate and compare the treatment outcomes associated with these two drugs:

(1) An investigator obtains only coded information on the treatment outcomes of patients treated for arthritis with Drug A versus Drug B from the patients' treating physician. The only involvement of the treating physician is to provide coded information to the investigator. The investigator and the treating physician enter into an agreement prohibiting the release of the key to decipher the code to the investigator under any circumstances, until the individuals are deceased. In this example, the investigator is not conducting human subjects research because the investigator cannot readily ascertain the patients' identity.

(2) An investigator obtains individually identifiable information on the treatment outcomes of patients treated for arthritis with either Drug A or Drug B by viewing patients' existing individually identifiable medical records at the clinics where the patients were treated. The investigator records the patients' treatment outcomes in a coded manner that could permit the identification of the patients. In this example, the investigator is conducting human subjects research because the investigator is obtaining identifiable private information from patients' (and now subjects') medical records. The study would not be exempt under 45 CFR 46.101(b)(4) since the investigator is recording the information in a coded manner, thus allowing the subjects to be identified indirectly through identifiers linked to the subjects.

(3) An investigator obtains individually identifiable information on the treatment outcomes of patients treated for arthritis with either Drug A or Drug B by viewing patients' existing individually identifiable medical records at the clinics where the patients were treated. The investigator records only patient age, sex, diagnosis, treatment, and health status at the end of 6 months of treatment so that the investigator cannot link the recorded information back to the patients. In this example, the investigator is conducting human subjects research because the investigator is obtaining identifiable private information from patients' (and now subjects') medical records. However, the study would be exempt under 45 CFR 46.101(b)(4) since the investigator records the information in such a manner that subjects cannot be identified either directly or indirectly through identifiers linked to the subjects.

Comparison to the HIPAA Privacy Rule

The Privacy Rule is a Federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 (see 45 CFR part 160 and subparts A and E of part 164). The Privacy Rule permits covered entities under the Rule to determine that health information is de-identified even if the health information has been assigned, and retains, a code or other means of record identification, provided that:

- (1) the code is not derived from or related to the information about the individual;
- (2) the code could not be translated to identify the individual; and

(3) the covered entity under the Privacy Rule does not use or disclose the code for other purposes or disclose the mechanism for re-identification (see HHS guidance entitled, *Institutional Review Boards and the HIPAA Privacy Rule*, page 6, Q and A #3, at http://privacyruleandresearch.nih.gov/pdf/IRB_Factsheet.pdf).

Regarding condition (1) above, in contrast to the Privacy Rule, information that is linked with a code derived from identifying information or related to information about the individual is not considered to be individually identifiable under the HHS regulations for the protection of human subjects at 45 CFR 46.102(f), if the investigators cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimen pertains. Therefore, some coded information, in which the code has been derived from identifying information linked to or related to the individual, would be individually identifiable under the Privacy Rule, but might not be individually identifiable under 45 CFR part 46.

If you have specific questions about how to apply this guidance, please contact OHRP by phone at (866) 447-4777 (toll-free within the U.S.), (240) 453-6900, or by e-mail at ohrp@hhs.gov.