

Best Practices for Postmortem Recovery of Normal Human Tissue for Research

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INTRODUCTION

Obtaining high-quality postmortem tissues appropriate for today's molecular and genomic research is one of the most challenging and logistically complex tissue acquisition problems for biospecimen resources and scientists. The NCI's mission includes the overarching goal to improve the ability to diagnose, prognosticate, treat, and prevent cancer and to develop novel therapeutics. Historically, many high-profile NCI initiatives, such as the Specialized Programs of Research Excellence (SPOREs), Early Detection Research Network (EDRN), The Cancer Genome Atlas (TCGA), and the Clinical Proteomic Technology Assessment for Cancer (CPTAC), have been significantly impacted by biospecimen availability and quality.

High-quality, well-annotated normal human tissues are essential to support the study of cancer and other diseases; therefore, better understanding and expeditious improvement in current methodologies for tissue acquisition are necessary to actualize the missions of the NCI and other research organizations. For example, a recently approved NIH Roadmap project, the Genotype-Tissue Expression Project (<http://nihroadmap.nih.gov/GTEx/>), requires large numbers of high-quality normal tissue samples to define and understand the differential nature of gene expression in the various tissues of the human body. In response to the current need, the NCI has undertaken the timely initiative to develop and disseminate these supplemental best practices aimed at improving acquisition ability and quality of normal human tissue for research.

Postmortem research tissues can be suitable for a broad set of research applications to support scientific and clinical discovery. Historically, however, there has been a lack of widespread knowledge and expertise in optimal recovery methods, challenging operational logistics, and misconceptions about the value of this collection modality and the types of research applications that could be supported by such tissues. If managed appropriately, postmortem tissue collection can meet current research demands and complement or, in some instances, serve as a surrogate for surgically acquired tissues from living donors in biospecimen research. With a proportionately higher potential yield in biospecimen quantities from a single donor than with surgical tissue recovery, postmortem tissues may help relieve some current constraints on biospecimen science, thereby speeding the development of new diagnostics and therapeutics.¹

This document focuses specifically on normal tissues obtained postmortem and highlights the current state of the science associated with postmortem tissue recovery and recommended best practices.

BEST PRACTICES FOR POSTMORTEM RECOVERY OF NORMAL HUMAN TISSUE FOR RESEARCH

A. Scope and Applicability

This document is intended to supplement the *NCI Best Practices for Biospecimen Resources*² and to support broadly the postmortem biospecimen collection efforts of the NCI (e.g., the Biospecimen Research Network, the Office of Biorepositories and Biospecimen Research [OBBR], and the cancer Human Biobank [caHUB]) and other organizations throughout the biomedical research enterprise.

In an effort to promote quality research using postmortem tissues, this document aims to define ideal, “best” technical, operational, and ethical practices for biospecimen resources, tissue banks, tissue recovery organizations (TROs), and research scientists seeking to work with postmortem tissues. The best practices and recommendations contained in this document offer guidance on topics that include donor identification and screening; tissue recovery; coordination of biospecimen collection; the preparation, storage, and processing of biospecimens and associated clinical data; and quality concerns related to advanced analytical research methodologies. These objectives are designed to support the long-term goal of harmonizing postmortem research tissue collection efforts with other preferred, evidenced-based biobanking practices.

As a result, this document focuses on the collection of normal control tissues from postmortem donors and the current state of the science associated with tissue recovery and recommended best practices. The concepts represented herein may be applied to other postmortem research tissue collection projects and may be adapted for research projects that focus on various disease states and tissue pathologies.

B. Overview of Sources for Postmortem Tissues

Postmortem tissue recovery and use follows a general sequence of events (appendix A) that typically begins through partnership with a variety of research tissue recovery programs. Such programs typically include rapid autopsy programs, organ procurement organizations (OPOs), TROs (tissue banks), and willed body donation programs. Other research partners may include medical examiners, funeral homes, and tissue collection networks. Each of these entities is discussed in the following section, and appendix B provides example areas of expertise for programs that are engaged in the recovery of tissue for research.

1. Rapid Autopsy Programs

Rapid autopsy (also called “warm” autopsy) is an autopsy performed soon after death for diagnostic purposes and with concomitant collection of tissues for research. The term “warm” derives from the short interval between time of death and acquisition of tissue samples during the autopsy when the donor body has not been refrigerated. The rapid

autopsy model, while historically focused on brain research,^{3,4} has expanded in recent years to include other disease types and research applications; e.g., metastatic prostate cancer, metastatic pancreatic cancer, idiopathic pulmonary fibrosis, fibromyalgia, and multiple sclerosis.^{5,6} The average postmortem interval (PMI) for these programs is 1 to 4 hours but may extend to 12 or more hours due to various logistical issues.

Due to the prerequisite infrastructure, funding, logistics, and time requirements involved to support these programs, only about a dozen rapid autopsy programs exist within the United States. Nonetheless, these programs present an invaluable opportunity to obtain high-quality research tissues. Established programs include those sponsored by the NCI SPOREs, the NIMH, and the National Institute of Child Health and Human Development (NICHD), some of which have been in existence for more than 25 years.⁷ Such programs are generally organized within academic medical centers and recover specialized tissues (e.g., prostate, brain, normal tissues, or metastatic cancers) for specific research projects that are difficult or impossible to acquire by other means.

With an infrastructure typically embedded within an academic medical institution and research framework, successful rapid autopsy programs have efficient operational planning. A successful rapid autopsy program requires significant planning to ensure adequate funding, skilled collaborative management, and a dedicated and passionate team of professional and donation coordination staff. A well-functioning rapid autopsy program requires a fully dedicated multidisciplinary team that includes attending physicians and residents, technicians, data managers, study nurses, and research coordinators who are well trained in donor recruitment and consent. All related staff should be trained in ethical and legal requirements and keep abreast of how procedural and legal requirements vary by institution and State.

The biospecimen recovery team is typically supervised by a pathologist, although pathology assistants and research technicians may be trained in gross anatomical dissection and tissue recovery methods with appropriate supervision. Rapid autopsy programs may have both a medical team and a tissue recovery team. Medical team members frequently include participating physicians, pathologists, pathology fellows, and pathology residents, whereas tissue procurement teams in this setting typically consist of pathology assistants, postdoctoral researchers, laboratory assistants, and residents. Most team members remain available by mobile phone or pager to ensure around-the-clock availability, and the team can be assembled for the autopsy through a pyramidal notification plan.

These programs are reviewed and approved by institutional review boards (IRBs). Permission for autopsy can be obtained before death via consent provided by the donor and/or authorization by next-of-kin (NOK) after the donor's death. In most cases, the donor is either hospitalized at the time of death or under hospice care. In cases where the patient dies outside of the hospital, the body is transported to the institution's morgue, which requires additional logistical planning and personnel and may increase PMI for tissue recovery.⁶

Many existing rapid autopsy programs are tissue specific (e.g., prostate, brain) and are supported by NIH grants to meet specific research needs. Successful partnership with a rapid autopsy program requires an individual at the host institution who recognizes the value of the partnership and is willing to contribute time and expertise.

2. Organ Procurement Organizations

The organ procurement system used in the United States developed during the past 40 years in a “bottom-up” fashion, starting with small independent and hospital-based programs. These programs have evolved into 58 OPOs that are federally designated by Centers for Medicare & Medicaid Services (CMS) to provide services for a specified donation service area. After 25 years of development and passage of the National Organ Transplant Act (NOTA) of 1984,⁸ the Organ Procurement and Transplantation Network (OPTN) was established. The OPTN is a unified, well-organized transplant network operated under Federal contract by the United Network of Organ Sharing (UNOS), a private, nonprofit organization. All OPOs, transplant programs, and histocompatibility laboratories in the United States are required to be members of the OPTN and abide by all of its policies and procedures.

OPOs typically recover solid organs such as the heart, lung, liver, and kidneys, among others, for transplantation into individuals suffering from end-stage organ failure and who are in need of an organ transplant to survive. Organ recoveries are typically performed on donors who die of some type of neurologic or anoxic injury. In addition to recovering organs, most OPOs are involved in recovering tissues such as bone, soft tissue, cardiovascular tissue, and skin for transplantation, and a significant number are also involved in recovering organs and tissues on behalf of other organizations for various types of research. The level of recovery activity of organs and tissue for research varies significantly across the OPO community.

The OPO system is ultimately funded by the CMS and insurers who pay for the transplants. The transplant center reimburses the OPO that performs the organ recovery procedure. The OPO is responsible for reimbursing the hospital where the organ recovery takes place for all hospital expenses related to the recovery procedure. All OPOs must conform to OPTN rules and regulations and all CMS regulations and performance standards. All OPOs are also members of the Association of Organ Procurement Organizations (AOPO), which offers a voluntary accreditation program. The accreditation program runs on a 3-year cycle, and a majority of the 58 established OPOs have been accredited by the AOPO.

Federal law requires hospitals to notify the local OPO of every death that occurs in the hospital and requires that the family be advised of its options to donate organs and tissue for transplant if the deceased has not made an anatomical gift. OPOs thus occupy a frontline position to approach families and obtain consent for research donation.

Generally, OPOs are open to seeking ways to acquire and provide research tissues, and CMS regulations that promote research tissue acquisition offer incentives to participate. However, these organizations may have limited experience and resources for research tissue procurement. With focused support and training, however, these organizations possess suitable infrastructure to recover research tissues.

3. Tissue Recovery Organizations (TROs)

Federal law requires all hospitals to have an agreement with a tissue bank and an eye bank to provide for the recovery of transplantable tissues in the hospital. There are approximately 80 TROs throughout the country that focus primarily on the collection of tissues for transplantation (e.g., bone, soft tissue, cardiovascular tissue, and skin). Approximately 90 additional organizations exclusively recover ocular tissue; i.e., corneas and sclera. The staff of a TRO is skilled in screening donors for relevant medical history and lifestyle risks, performing aseptic recovery procedures using sterile supplies, excising tissue in a professional manner, and packaging recovered tissue appropriately for delivery. Tissue recovery staff receive training in quality assurance concepts, and the tracking and trending of specific quality performance indicators are standard.

TRO staff are intimately familiar with following written protocols and maintaining quality standards. Typically, recovery team leaders and other team members include current or former surgical technicians, paramedics, physician's assistants, emergency medical technicians, or nurses who have been trained, passed extensive written exams, and been awarded the professional designation as Certified Tissue Banking Specialists (CTBS) by the American Association of Tissue Banks (AATB). Although some technicians may not be certified, they generally perform the recovery under the supervision of a certified team leader. TROs manage their recovery operations in various ways, using full-time staff, per diem staff, or a mixture of the two. Depending on logistics and collection-site relationships, TROs can recover tissue in a hospital operating room or their own recovery suite. Occasionally, some will recover tissue in a morgue setting, although (per standards and guidance published by the AATB) any tissue recovery site must qualify by meeting specific parameters that prevent contamination.

Most TROs work with long, but defined and limited, ischemia times that are typically within 24 hours of asystole. Recovered tissue is typically shipped at wet-ice temperatures to a tissue processing establishment soon after completion of the recovery procedures. On average, tissues collected by TROs experience approximately 48 overall hours of ischemia prior to further preservation methods. All TROs have experience working current good tissue practices (cGTP)⁹ in accordance with FDA regulations codified within 21 Code of Federal Regulations (CFR) 1271.

Currently, few TROs routinely recover low-PMI tissues for genomic and proteomic research applications; hence, most do not have staff extensively trained in these requirements. With focused support and training, however, these organizations possess suitable infrastructure to recover research tissues.

4. Tissue Collection Networks

Tissue collection networks typically comprise managed networks of partner institutions (e.g., nonprofit organizations such as OPOs and TROs) that handle the placement of organs and tissues that may have been collected initially for transplant but are later determined unsuitable for that purpose. These groups also prospectively recover a variety of biospecimens for research, including healthy and diseased/tumor tissues and fluids. For example, these groups provide fresh human pancreata for the isolation and further manufacture of islet cells; fresh human livers for hepatocyte preparation; or other cells, organs, or tissues to approved researchers for mostly nonclinical investigative purposes. These organizations may also provide stem cells from cord blood and adult bone marrow that may be eventually used in clinical studies. Some specialized research service groups focus on collecting fresh frozen or formalin-fixed paraffin-embedded (FFPE) tissues for research purposes and maintain commercially available inventories of these biospecimens.

Tissue collection networks have existing collection site relationships that can be accessed to meet research tissue needs. These groups are accustomed to working within contract specifications, and close relationship management may promote standards of quality and productivity and to ensure adherence to standard operating procedures (SOPs).

5. Willed Body Donation Programs

Willed body donation programs, which were originally created to advance medical education, science, and research programs, may be similar in design to rapid autopsy programs. Typically coordinated through university medical school programs, donor recruitment may occur prospectively from the community via formal outreach or directly in the hospital setting through direct contact with the individual's attending physician and/or medical team. In the community setting, outreach assistance may be supplemented by mortuary partners. Recruitment may also occur retrospective to death through familial and/or guardian authorization. In recent years, the willed body donation operational model has been expanded to the research institute setting in an effort to support biospecimen-based research.

The donation process involves completion of consent and other forms (online or in person). Once the donation is formally registered, the individual receives a donor card. Donations come into effect upon notification of death. Donors under 18 years of age require a signature from the individual's parent or guardian, and the donation consent must be signed and witnessed by two other persons at least 21 years of age. Consent may also be offered at time of death, providing that two witnesses are available. Anatomical donations may also be revoked orally or in writing. Family members may authorize donation if the individual cannot communicate, and statutes exist as to which persons may do so. Consent involves authorization of transport of remains, approval for

processing and/or removal of organs and tissues, and relinquishment of rights and claims to the body. Conditions that may render donations unacceptable include:

- Extensive surgical intervention preceding death resulting in damage ante- or postmortem;
- Notification of death occurred 72 hours or more after autopsy;
- Donor suffered from an infectious disease;
- Donor weighed more than 300 pounds; and/or
- Death occurred outside the state/region of authorized program operation.

Typically, the body donation program will absorb costs related to transportation, embalming, and cremation. Key logistical considerations encompass the timely notification of death, transportation of the body, recovery of tissues, processing of tissues, and appropriate disposition of remains. Thus, an allowable time period for retention of the body should be planned. When research is completed and/or appropriate tissues have been recovered, the body is prepared and returned to the family for burial or cremation. In some cases, the donor is offered a “Special Disposition of Body Request Form” to specify any special needs and/or wishes related to the pre-interment care of his/her remains. Typically, details of the utilization of organs, tissues, and body parts remain confidential and are not disclosed to the family. While some institutions manage and operate such programs on their own,^{10, 11} a number of states centrally manage the Human Gift Registry program so that donated bodies can be obtained from a number of source sites and distributed equitably among other in-state or regional medical education centers (for an example, see the Commonwealth of Pennsylvania’s Humanity Gift Registry).¹²

While these programs may be suitable to collect research tissues in some instances, the objective of Human Gift Registry programs is not aligned with the needs of research tissue banking. The PMI for willed body donors is typically long and quite varied, largely due to the unpredictable nature of the donation and body preparation process. Therefore, tissue collection for research use is generally not compatible with Human Gift Registry programs.

6. Medical Examiners and Coroners

Typically, any individual who dies unattended by medical personnel or due to an injury comes under the jurisdiction of a medical examiner (ME) who is an official, usually a physician, authorized by a governmental unit to ascertain causes of deaths, especially those not occurring under natural circumstances. An individual who dies unattended may also come under the jurisdiction of a coroner, who is an officer of a county or municipality whose chief function is to investigate by inquest, as before a jury, any death not clearly resulting from natural causes. Typically, 25 percent of the deaths in a state are initially referred to an ME or coroner. Half of these cases are pronounced dead on the scene and transferred directly to the ME or coroner’s office without admission to an acute medical care facility. Potential donors can be identified among this population onsite at the ME office or via access to case information at the ME’s office. ME cases that are first

taken to acute medical care facilities may be identified as donors through local OPO or TRO programs. In these cases, it is still necessary to obtain permission from the ME's office before tissue recovery can commence, thereby necessitating a close working relationship between the ME office and the tissue recovery group.

Many MEs are members of the National Association of Medical Examiners (NAME), which inspects and certifies ME facilities. It should be noted, however, that not all ME facilities are accredited by NAME. Donor recovery at ME and coroner offices typically has a PMI of 12 to 24 hours and, therefore, may be unsuitable for low-PMI research tissue recovery projects.

MEs and coroners typically do not have the appropriate level of resources to participate in research tissue recovery. Providing research tissues, which may be viewed as a high-risk practice, is prohibited by some ME offices; e.g., Massachusetts and, likely soon, New York. Timing for tissue collection will be determined by the ME, and the combined last seen alive (LSA) and PMI times are often lengthy. MEs and coroners must prioritize medico-legal issues over the needs of tissue recovery for transplant, and caseload/staffing issues often limit resources. Although some of those deceased at the ME office may be good donation candidates (i.e., young, accidental death victims), typically they are poor candidates for high-quality research tissue recovery due to lengthy PMIs, drug abuse, or tissue damage as a result of injury. Associated clinical data may be difficult to obtain or unreliable, and the regulations of the individual ME offices may hamper implementation of SOPs from an external organization. However, some of these difficulties may be overcome through a close collaborative relationship between an OPO and the ME.

Some tissue collection programs have forged successful relationships with MEs and have received access to specific types of tissues, such as brain. However, in view of their mission and method of operation, many MEs may not be consistent sources of systematic and controlled biospecimen recovery to support research needs.

7. Funeral Homes

Funeral homes serve a role in postmortem recovery as research partners that may assist with donor availability notification. Ideally, partnering with a funeral home requires requisite planning and transparent, timely, and regular communication and education. In general, however, funeral homes provide inadequate environments for systematic and controlled research tissue recovery. As such, some states (e.g., New Jersey, North Carolina) have banned research tissue recovery in this setting. Furthermore, funeral homes typically collect and transport the deceased in timeframes that result in a lengthy PMI, thereby making these tissues suboptimal for research. Funeral homes are accustomed to working with OPOs and other tissue recovery organizations. However, some research tissue needs could potentially compete with OPOs in terms of timing and priority of collection. Funeral homes also typically seek reimbursement for their efforts and will have limited access to reliable clinical data.

As the Harvard Brain Tissue Resource Center has demonstrated, a successful partnership with a funeral home requires a direct relationship with the home's director, who may do some of the specific tissue recovery work him/herself. Therefore, it is recommended that funeral homes be engaged to facilitate donor recruitment and notification but not to directly conduct tissue recovery. Funeral homes offer support in ensuring that the donor's end-of-life wishes are carried out appropriately in conjunction with tissue recovery.

8. Other Sources of Normal Tissues

Although this document focuses exclusively on issues related to the acquisition of normal tissues from postmortem donors, it is important to mention that certain high-quality normal tissues for research can be easily obtained from living donors, including those undergoing surgical procedures.

C. Technical Best Practice Considerations

1. Number of Donors (Cohort Size) and Study Power

Historically, statistical sampling has not factored prominently into the design of studies utilizing postmortem tissues. Major factors to consider for postmortem research tissue collection include the number of unique donors required for statistical significance and the overall timeline for study completion. Although each research project has unique sample accrual goals, the size of the study group often correlates with the statistical significance of results. The overall scale of collection (number of donors) in combination with selection criteria (probability of encountering a donor) and donor network size should be factored into calculations for the overall time required to recover materials from sufficient numbers of donors. To ensure optimal use of postmortem tissues, it is recommended that a biostatistician be consulted when possible.

2. Defining Donor Selection Criteria

It is recommended to define donor inclusion and exclusion criteria well ahead of the research tissue recovery process. Understanding the criteria that OPOs and TROs use for transplant can help inform the criteria used for screening research donors.

Although consistently rigorous, criteria for recovering organs for transplant may vary depending on the transplant program, transplant surgeon, potential recipient, and the potential recipient's clinical condition at the time of transplant. Criteria for a medically suitable organ donor are broad, and a set of medical acceptability criteria can provide a high degree of confidence that the transplanted organ will survive and function in the recipient. Exclusion criteria for organ donors typically include conditions such as Human Immunodeficiency Virus (HIV) and certain septic infections. Ultimately, however, the transplant surgeon decides on the patient's behalf whether to accept or reject an organ for transplantation. The Centers for Disease Control and Prevention (CDC) has issued guidelines and criteria to determine if an organ donor is considered high risk for disease transmission. These guidelines do not prohibit the use of high-risk donors for organ

transplantation. National transplant program regulations require that the potential recipient must be informed of the clinical risks if a high-risk donor is utilized by the transplant program.

For recovery of transplantable organs, donors are typically assigned to general categories such as (i) standard criteria donor (SCD) - this includes donors up to 60 years of age with no comorbidities; (ii) extended criteria donor (ECD) - this includes donors 60 years of age and above or donors 50 to 59 years of age with comorbidities; and (iii) donation after cardiac death (DCD) - that is, a death declared on the basis of cardiopulmonary criteria (i.e., irreversible cessation of circulatory and respiratory function) rather than the neurologic criteria used to declare “brain death” or the irreversible loss of all functions of the entire brain, including the brain stem.¹³

To fully assess donor suitability for a given research project, specific inclusion and exclusion criteria should be established on a per-project basis. Developing broad criteria is optimal for increasing the number and diversity of potential research tissue donors. For normal postmortem tissue recovery, specifying general criteria and exclusions for certain medical conditions enables donor prescreening. This strategy may, however, require that donors who lack the required medical information be excluded from consideration. Ultimately, broadening the screening criteria enables donation opportunities and provides recovery organizations and researchers with a larger pool of potential donors from which to choose.

Useful categories of information that can be used to define donor inclusion criteria for normal research tissue donors are provided in appendix C.

Example scenarios for collecting normal research tissues postmortem are illustrated through case studies in appendix D.

3. Defining “Normal” and “Control” for Research Donors and Tissues

“Normal” or “control” tissues for research can include multiple assorted reference tissues from the human body that are used to test gene and protein expression or cross-reactivity across different organ systems and tissues. “Normal” tissues for research commonly refer to tissue types corresponding to organs frequently afflicted by cancer or other diseases and that are recovered from individuals free of the given disease. The terms “control,” “experimental control,” and “comparator tissue” are also appropriate to use when generically defining donor and tissue parameters in the context of postmortem research tissue collection. Moreover, it should be noted that a broad label such as “normal” may be less useful than a relative definition in the context of specific research interests.

The criteria for categorizing normal tissue and donors can be complex and nuanced, as controls vary among types of research studies and populations. The ultimate definition of “normal” for the purpose of a control tissue depends on the specific interests of the

research being conducted. Normal control tissues may therefore be broadly characterized according to three general levels:

- **Molecular Profile.** A tissue sample may be labeled as “normal” based on having no detectable evidence of disease in the range of sensitivity of a specific diagnostic test that has been conducted on it.
- **Morphology and Histology.** A tissue sample devoid of macroscopic and microscopic (pathological) evidence of disease may be labeled as “normal.” With this approach, however, it is helpful to differentiate between the localized pathologic assessment of disease and systemic processes such as diabetes or cardiovascular disease.
- **Donor Medical History.** A tissue sample may be labeled as “normal” if it comes from a donor with no history of chronic or acute disease. It should be noted however, that a comorbidity does not necessarily indicate an exclusionary criterion for some research studies. For instance, individuals who die from cardiovascular events may be considered excellent donors for normal control tissues for cancer research.

4. Postmortem Interval (PMI)

The PMI is defined as the difference between the time that death is declared (if death occurs in a hospital or under the direct observation of medical personnel) or the time the donor is LSA and the time that research tissue is preserved (frozen, fixed, etc). The designation “time to preservation” is often also used in the context of research tissue collection to denote the time elapsed from cross-clamping (cutting off blood supply to the tissue to be excised) and tissue stabilization or preservation: i.e., immersion in fixative or freezing. The maximum acceptable PMI should be clearly defined for each research tissue collection project. Typically, projects with a low-PMI criterion will collect and preserve biospecimens within 1 to 6 hours. The maximum PMI for most research tissue collection projects is typically 24 hours. With respect to research tissue recovery, every attempt should be made to recover tissue as quickly as possible following death of the donor, as speed is a factor for preserving tissue quality. Therefore, timing variables must be carefully documented. It should also be noted that speed should not compromise staff safety, the use of universal precautions, or the condition of the biospecimens.

In general terms, PMI is inversely related to macromolecular integrity such as RNA quality. That is, the longer the PMI until tissue sample stabilization (freezing), the poorer the RNA quality. However, the effects of PMI on RNA quality can vary significantly between different organs and tissues of the human body and may be less important than some other factors, such as donor agonal state.

Cold storage of postmortem donors after death may improve research tissue quality and extend the allowable PMI for the recovery of tissue samples of suitable quality for research. In the absence of cold storage, cooling blankets may also be used postmortem.

5. Preparation of the Donor for Recovery

It is crucial to note that preparing the donor for recovery should not interfere or impede end-of-life considerations such as viewing of the body and/or interment. Postmortem research tissues should be collected using standard necropsy methods and include aseptic methods to the extent possible. To prevent contamination, especially when collecting fresh viable tissues for tissue culture experimentation, it is optimal to prepare the donor body by first spraying with 70 percent ethanol or another appropriate disinfectant solution. Solutions used in this process should not contact the target tissues for research. Separate sterile blades should be used for tissue dissection and sectioning.

When recovering tissues from the body cavity, the internal organs can be accessed through an anterior, “Y-shaped” incision, made from the bilateral clavicular joints and extending to the pubis. The skin and subcutaneous tissues may be retracted from the thorax and abdomen and the sternum removed. The internal organs, from the larynx to the pelvis, can then be dissected from their posterior attachments to the body and the diaphragm freed from its peripheral attachments. While still in continuity with the body, the rectum should be cross-clamped to prevent spillage of intestinal contents into the pelvis and abdominal cavities. After the dissection of the pelvis, the rectum can be transected and the viscera removed *en bloc* for further dissection and processing for research use.⁶

6. Tissue Recovery in the Context of Funeral, Burial, and Family Requirements

OPOs and TROs are acutely aware of the necessity to preserve donor body integrity as much as possible so as not to impede funeral arrangements. Various techniques and tissue recovery approaches are used to ensure that the donor’s body is restored in a way that is suitable for funeral and burial arrangements.

Appropriately trained technicians can readily remove the brain, eyes, and internal organs for research while protecting the integrity and appearance of the deceased body so that an open-casket funeral is possible. For example, prosthetics can be placed in the eye sockets after the recovery of ocular tissues. Recovery of the long bones is also possible, since that part of the deceased body is generally not viewed at funerals. To preserve the integrity of the body form, prosthetics typically made of polyvinyl chloride (PVC) pipe are placed where donated bone was removed. Removing the temporal bone with internal and middle ear structures intact is also feasible with the use of appropriate reconstructive techniques. Cremation rather than interment of the donor’s remains typically allows for more extensive recovery of research tissues.

Brain donation is compatible with open-casket funeral arrangements. An incision is made to remove the calvarium and access the brain for removal, and the donor's hair is used to hide the scalp sutures from view. This approach is not recommended if the donor is bald, although a careful recovery by a skilled technician and other funeral home cosmetic techniques can be employed to conceal the sutures from view.

7. Biospecimen Containers, Recovery Kits, and Supplies

Appropriate containers that can be labeled and can withstand ultra-low temperatures should be used to collect and store frozen tissue samples for research. Standard cryovials (1.0 to 2.0 mL or larger) may be used to collect and store frozen tissues long-term; however, the removal of frozen tissue from cryovials can be difficult. Conical tubes (15 to 50 mL) may also be used for frozen tissue storage. Standard-sized histology cassettes are recommended for the collection of formalin-fixed tissues and may also be used to collect and store frozen tissues, although the cassettes' perforated exteriors may contribute to sample cross-contamination as small tissue particles may pass through the opening in the containers. Additionally, the use of standard histology cassettes (which are not air-tight) to store frozen tissues may contribute to tissue sample desiccation.

Other container options include a large-size version of the histology cassette for the collection, freezing, and storage of larger tissues samples such as quadrant brain slices or whole organ sections. Molded plastic containers known as "clamshells" and "cryosettes" and small screw-top aluminum canisters may also be used to store frozen tissue.

Proper labeling of specimens is essential. All biospecimen storage containers should have a surface location where a unique identification number (optimally including a one- or two-dimensional barcode) can be printed or an appropriate adhesive label applied. If barcodes are not printed on biospecimen containers, it is possible to obtain in bulk preprinted adhesive labels with unique barcodes. An adhesive label applied to a biospecimen container should be tested in advance for its ability to withstand liquid nitrogen, dry ice, and various tissue fixation and processing solvents.

The preproduction and provision of fully contained research tissue recovery kits can greatly facilitate postmortem recovery and reduce collection time intervals. These kits should optimally contain all necessary disposable supplies such that they can be opened on a back or side table of an operating room or morgue and provide what is needed to carry out the full recovery. These kits, which can be customized, commonly contain personal protection gear (e.g., smocks, gloves, face masks, booties), disposable scalpels, knives, blades, absorbent pads, and waste bags. A list of recommended postmortem research tissue recovery kit contents and assorted supplies is provided in appendix E.

8. Defining Biospecimen Collection Sets (Tissue Panels)

Maximizing the yield and quality of tissues recovered from each donor while maintaining the respect due to the donor should be the primary objectives of postmortem research tissue recovery. These goals can be attained by collecting a large number of samples from one donor as part of a single research protocol or by combining multiple compatible research tissue collection protocols where appropriate. Frequently, postmortem research tissue recovery projects (in particular, normal tissue collection) specify the collection of a wide assortment of different tissues from a single donor.

To organize the recovery of multiple tissues from a single donor, it is helpful to clearly define and prioritize the list of tissues that should be targeted for collection. Appendix F provides example sets of commonly collected normal control research tissues. The example set provided, known as a “multi-tissue survey,” includes more than 50 different tissues from a single donor. It is also important to note that multiple tissues should be prioritized for collection based on the requirements of a research project and organized according to anatomic or body regions to maximize efficiency during the recovery process. Also, tissues may be collected in a sequence such that those with the most labile macromolecules are obtained first and those most stable are collected last. Recovery of tissues and organs for transplant always should take priority over collection for research.

9. Collection of Solid Tissue Biospecimens

While biospecimen collection, preparation, and packaging requirements may vary per research protocol, it is recommended that standardized collection methods for different tissues be used to the extent possible. Standards should be considered for frozen and FFPE formats without limiting the range of suitability for downstream research applications. Frozen and FFPE postmortem tissues for research (for biobanking and future use) are typically collected in 0.5- to 2.0-gram or larger aliquots. Although samples of this size may be slightly larger than biopsy-sized samples collected routinely by pathologists for diagnosis in the autopsy setting, they are in general smaller than those most commonly collected by OPOs and TROs for transplant purposes. Samples of this size are sometimes referred to as “snippets” of tissue.

An approach to collecting multiple replicate samples of standard size can be applied to nearly all tissue types if tissue volume is adequate. However, not all organs and tissue types may permit such replicate sampling. Organs such as the brain require carefully categorized collection strategies along with skilled, fine dissection of various neuroanatomical sub-regions and structures. Vonsattel and colleagues have published well-defined protocols for the collection of brain tissue.¹⁴

Furthermore, it may be useful to collect research biospecimens in mixed formats where one sample may be frozen and a portion of adjacent tissue is prepared as an FFPE sample. This approach may enable additional downstream research use for the tissues. Quality control on representative FFPE sections should include timely post-recovery

morphologic and histopathologic review. Biospecimen collection and preparation guidelines are provided in appendix G.

1. Frozen Tissues

Snap-freezing tissue samples in liquid nitrogen is a common method for preserving RNA, DNA, and proteins for genomic and proteomic research. When collecting frozen tissues, the objective is to preserve tissue RNA, DNA, and protein as close as possible to its state in the living individual. Following initial snap-freezing in liquid nitrogen, frozen tissue samples can be transferred to dry ice for temporary storage.

2. Optimum Cutting Temperature Compound (OCT)-Embedded Tissues

Collection in OCT is intended to preserve tissue morphology in addition to RNA, DNA, and proteins and is frequently performed by freezing OCT-embedded tissue in a dry ice–chilled isopentane bath. Isopentane’s volatility, however, renders this method difficult to practice in the field.

3. Fixed Tissues

Fixing tissues in neutral buffered formalin is a common method of preserving tissue morphology and antigenicity. Tissue can be temporarily stored in formalin until transported to an appropriate facility for processing and the preparation of paraffin blocks.

4. Fresh Tissues

Fresh tissues are commonly collected and used to prepare isolated live cells for tissue culture–based experiments. For these types of applications, a variety of liquid transport media can be used to maintain a majority of the cells within the tissue sample in a biologically viable state.

Live, viable tissues for research applications are commonly collected in tissue culture media that is available in a variety of formulations with or without antiseptic or nutritional supplementation. These types of fresh-tissue media are typically provided in sealed, sterile 250 to 500 mL bottles and are commonly refrigerated once opened. It is optimal to maintain a refrigerated and fresh, unopened supply of tissue media at each recovery facility so that it is ready for use. Supplementing tissue media in advance can save time. If advance supplementation is impractical, preparing premeasured and labeled additives in advance can save time when recovery teams are mobilizing.

10. Collection of Blood and Other Biofluids

Whole blood can be collected into various types of tubes, shipped at ambient or refrigerated temperatures, or processed locally prior to delivery. Whole blood can be shipped under refrigerated conditions using blue ice or gel packs within insulated shipping boxes. Blood delivered for serology testing is typically shipped at ambient temperature. Although wet ice is commonly used in procedures such as transplants, blood delivered for research applications or biobanking may require more controlled shipping temperatures using blue ice or gel pack inserts to maintain refrigerated conditions within the shipping box.

At the time of postmortem recovery, blood can be collected for both serology and toxicology testing and for research purposes. If the donor is not a transplant donor, additional samples of blood for serology testing are helpful, since information about the donor's infectious disease status obtained from NOK or historical medical record may be inaccurate.

Researchers should be aware of the issue concerning potential “double testing” of donor blood for infectious diseases. All organ and tissue donors for transplantation will undergo serology testing, the results of which can be provided to researchers. In the event that a research project requires serological testing beyond the supporting OPO or TRO protocols, “conflicting test results” may create significant potential implications for the transplanted organs or tissues. In this circumstance, it is best to notify the tissue provider who in turn will notify the hospital that may have received transplanted organs or tissues. This additional information may affect patient care, medical counseling, and the research staff who have handled organs or tissues. Appendix G describes commonly used methods and tubes for research blood collection.

11. Temporary Storage of Recovered Biospecimens, Transport, and Shipping Methods

Storage capabilities vary among OPOs and TROs. Most postmortem tissue recovery agencies have temporary storage capabilities and are accustomed to shipping tissue to the user immediately after recovery. Some have temporary storage capabilities of 72 hours or less, while others have more sophisticated and longer-term storage capabilities.

Although the shipping of biological materials within the United States and internationally follows straightforward regulations, delivery procedures depend on the courier. For example, many commercial couriers pick up shipments during normal weekday working hours but do not typically top-off dry ice should a frozen tissue shipment be delayed. By contrast, specialized express couriers offer more expensive but specialized pickup and delivery service around the clock. These companies also offer a service of dry ice top-off for frozen shipments if necessary and are accustomed to handling fresh tissue and liquid biomaterial shipments. OPO and TRO tissue collection sites are generally experienced with shipping issues as they ship to tissue processors on a daily basis.

12. Biospecimen and Data Quality Control

Quality control (QC) measures should be defined clearly with regard to postmortem research tissues. In many instances, however, no formally validated consensus of what constitutes a quality sample exists. Despite the lack of formal guidelines, it is recommended that minimal QC measures include:

- Review of sample collection and storage processes
- Histological review of samples to assess proper biospecimen identification
- Molecular quality (RNA) review of specimens
- Donor clinical data review.

It is recommended that some minimum number of samples (if not all) should undergo QC review, which may be coordinated as a retrospective review of a defined percentage of recovered samples or cases.

1. Biospecimen Histologic Quality Control

Research tissues collected postmortem should be examined macroscopically at the time of collection and microscopically based on prepared hematoxylin and eosin (H&E)-counterstained slides to confirm that the sample accurately represents the desired tissue type and to confirm whether the tissue biospecimen demonstrates observable presence or absence of disease (pathology verification). In the case of normal postmortem tissue collection, this review ensures that the tissue is characterized as to the presence or absence of any observable pathology or evidence of disease. Grizzle and colleagues offer recommendations for such pathologic review,^{15, 16} which may be completed any time following biospecimen collection, either on demand to fill research requests or on an ongoing basis so that samples are annotated with this information early in the process.

Utilizing FFPE samples for this pathology review and assigning the final sample diagnosis to the adjacent frozen sample is a convenient method of confirming sample histology. H&E-counterstained slides can be prepared from FFPE samples. The use of FFPE samples alone for histology QC avoids the preparation of H&E slides from frozen samples or OCT samples, which can be more difficult for histotechnologists to work with and may offer suboptimal morphology for review and diagnosis.

2. Biospecimen Molecular Quality Control

Myriad molecular assays may be performed on tissue-derived analytes, including genomic, epigenomic, proteomic, and metabolomic assays to assess DNA, RNA, and proteins in tissues, serum, and plasma. Although factors that affect relevant QC variables may vary across each assay and analyte combination, relatively few formal studies have been carried out to understand these factors in detail. RNA, for example, is a relatively labile molecule that is subject to rapid degradation, so the integrity of RNA extracted from frozen postmortem research tissues has traditionally served as a surrogate for

overall tissue quality and suitability for genomic, proteomic, and other analyses. Depending on specific research objectives, macromolecules such as proteins and methylated DNAs may also be integral to biospecimen quality.

RNA quality is frequently assessed using the ratio of the areas under the curves of the 28S:18S ribosomal fractions after electrophoresis. Using this method, intact RNA has a ratio of approximately 2.0. A variation on this approach uses the RNA integrity number (RIN) or score, which is based on the use of algorithms and equipment manufactured by Agilent Technologies[©].^{17, 18} RNA quality increases as the RIN value approaches 10. In general, samples with a RIN value of 7 or above are considered of good quality.¹⁹ Recent reports suggest that RIN may be a better measurement of brain tissue quality than pH, PMI, or protein content¹⁹ and that there appears to be no direct correlation between RIN and a PMI of less than 40 hours.^{19, 20}

RNA quality may vary among tissue types, and the lower cutoff for RIN values will vary according to the goals of the research project. Factors affecting RNA quality in brain tissue are the most extensively studied, and results suggest that acceptable quality may be obtained 24 hours or more postmortem.²¹ However, agonal factors and other antemortem factors (hospitalizations, coma, respiratory illness, use of artificial ventilation, coma, hypoxia) may be as important as postmortem factors.^{21, 22}

Gene expression analysis and epigenetic markers have also been explored to evaluate molecular quality by factoring relevant quality correlates as an indicator of overall quality. Miller and colleagues observed that the following factors have a demonstrable effect on gene expression and overall quality: pH, age, PMI, and length of time in storage.²³ Emerging research suggests, however, that a donor's agonal state may impact tissue quality more significantly than PMI.^{19, 24-27} Tissues from donors with prolonged agonal states (e.g., prolonged active death/natural death phases) should be excluded if optimum RNA quality is a principal consideration. If tissue is recovered from donors with prolonged agonal states, PMI should be appropriately documented and tissue quality assessed. This information should be made available to researchers interested in utilizing such tissue.

Brain pH can be a major indicator of brain tissue quality for genomics research.^{21, 25, 26, 28-31} Perhaps not surprisingly, brain pH is affected by agonal state; a prolonged agonal state correlates with lower brain pH.²⁷ The strong effects of antemortem parameters on brain pH led Hardy and colleagues to develop a four-point rating scale (table 1),²⁵ with a score of 1 representing the highest brain tissue quality for RNA studies.^{25, 27, 32}

It should be noted that information to determine the Hardy scale is not necessarily recorded for all potential postmortem donors, so logistical considerations need to be made or Hardy scale variables included in the recommended minimal dataset.

Table 1. The Hardy Scale: Categories of Agonal Duration²⁵	
Category	Description
1: Violent and fast death	Deaths due to accident, blunt force, trauma or suicide, terminal phase ≤ 10 min.
2: Fast death, natural causes	Sudden unexpected deaths of people who had been reasonably healthy, after a terminal phase estimated at < 1 hr (with a myocardial infarction as a model cause of death)
3: Intermediate death	Death after a terminal phase of 1 to 24 hrs.
4: Slow death	Death after a long illness, with a terminal phase longer than 1 day

Tomita et al. have found that coma and hypoxia affect RNA integrity and gene expression profiles.³² Appendix H provides an extensive list of variables that may affect the quality of postmortem research tissues.

It should be noted that translational medicine approaches will likely require additional measures of protein integrity. As gene expression and epigenetic markers of disease are explored more fully, proteomic analysis will play a larger role in determining tissue quality and suitability for purpose. Some proteins, especially those involved in signal transduction, are more susceptible than RNA to degradation postmortem. Protein quality will likely be important in studies of cancer-related molecular events involved in carcinogenesis, invasion, and metastasis.

3. Data Quality Control

It is important to ensure that information provided on postmortem donors and their recovered samples is complete and accurate. The accuracy of all data should be confirmed through reviewing inpatient and outpatient medical records when available, including those from the terminal hospitalization. This review is especially important if infectious disease such as HIV, tuberculosis, and hepatitis is to be recorded. Dedicated staff who are well trained in data abstraction are essential to this process. In addition, all blood tests should be confirmed through laboratory record review, and consent documentation should be included in the database if possible. The clinical data database, if utilized, should be subjected to periodic data monitoring and QC audits. Furthermore, this process must be carried out in a manner that ensures patient confidentiality and protection in compliance with the Health Insurance Portability and Accountability Act (HIPAA) guidelines. Potential data for postmortem research biospecimen recovery and QC are provided in appendix I.

D. Logistics and Operational Best Practices

1. Donor Screening and Identification

By law, all deaths in hospitals must be reported to the local OPO. Most OPOs and hospitals seek to have deaths reported within 1 hour although hospital compliance with this Federal regulation varies significantly across the Nation. Following notification of the death, the OPO then begins to evaluate the patient as a potential donor for organ and tissue transplant. A few OPOs and TROs nationally will also assess the capacity of a deceased patient to donate for research, education, or other types of therapy. The deceased patient's donation potential is determined by the cause and manner of death in addition to the decedent's known medical and behavioral history.

OPOs and TROs typically have call centers with trained staff to screen and discuss donation options with families. Donor screeners (e.g., at the call center) may be the first to rule out potential donors based on specified exclusion criteria. For patients who die in a hospital setting and are eligible for organ donation, the OPO first will approach the NOK to request that he/she authorize an anatomical gift from the decedent. When patients are not suitable for organ donation, an OPO or TRO will usually first approach the NOK via telephone to request an anatomical gift. All organizations that screen and recover tissues for transplantation are subject to FDA regulations set out in 21 CFR-1271. As part of the organ and tissue recovery process, blood is required to be drawn for various clinical tests, including blood cultures. In organ recovery, other clinical tests may also be performed, including biopsies, bronchoscopies, x rays, cardiac catheterization, and a battery of other clinical tests. Section 2 of the UNOS Policy 2.0: *Minimum Standards for Organ Procurement Organizations*³³ lists requirements for testing of all organ donors.

OPOs and TROs prepare a medical and behavioral history document to evaluate potential donors for diseases and to determine the general health of the donor. The history generally includes questions about medical conditions, prescription drug use, alcohol and recreational drug abuse, smoking history, travel, and lifestyle. In the course of the donor evaluation post-recovery, TROs may also contact other NOK and primary care providers to collect additional medical information required to determine donor medical suitability. Criteria will vary by TRO and will be based on FDA regulations, AATB standards, and the established criteria of the requesting/receiving organization. Before recovering research tissues, it is recommended that donor selection criteria be published.

Donors will be screened by qualified staff prior to approaching a family for consent. The level of screening will depend on existing criteria. All TROs have medical directors available as a resource for determining donor suitability. All referrals are documented, and all documents related to consent and medical screening are placed in a donor chart and retained by the TRO in accordance with Federal and State laws and AATB standards. If a family decides that it wants to donate tissue for research, the family must understand the process and potential use of the tissue.

Individuals with an extensive drug use history, needle tracks, infectious diseases, recent onset and rapid progression of dementia (as seen with Jakob-Creutzfeldt disease), and potential forensic complications are excluded as donors of transplantable tissues. Generally, the donor criteria used by OPOs for whole-organ acceptance are typically stricter than the criteria necessary for research tissues. For example, whole, fresh liver recovery may require full serological testing on the donor to confirm that the donor is free of hepatitis, HIV, and human T-lymphotropic virus (HTLV) whereas this may not be necessary for frozen samples for research.

The donor chart and history should always be reviewed a second time prior to recovery to ensure that the donor meets the criteria. Information provided to donor screeners by donor families is not always reliable, as these NOK are typically in various stages of mourning and are under great emotional stress.

2. Recovery Team Communication and Workflow

Recovery team training, timing, and coordination are major issues to be addressed in the recovery of organs and tissue for research. Per diem recovery technicians are able to travel quickly to the recovery site to obtain additional medical records and perform tissue recoveries. Many of these teams have immediate access to an on-call clinical coordinator and a board-certified pathologist if needed to determine donor suitability.

All tissue recovery organizations maintain medical records, and skilled staff can obtain additional records as necessary. Pathologists are available for consultation. Many OPOs also have professional services staff that provide training to hospitals on donation protocols and regularly monitor the donor notification systems to ensure that they operate according to expectations.

Tissue recovery team leaders are trained and qualified to make recovery decisions. These individuals call other team members, arrange for the recovery site, and coordinate the actual recovery of tissue with hospital staff, MEs, and other interested parties. These staff members are trained in donor screening, sterile procedure, tissue excision, packaging, and documentation practices. Timing is one of the most crucial and logistically complicated factors in postmortem research tissue recovery, and the time required for each stage in the recovery process may vary significantly.

Postmortem tissue for transplant is typically recovered within 24 hours. In most cases, the screening and authorization process takes at least 2 hours, although more time may be required to locate the NOK. For instance, after notification of donor death, it typically requires 2 to 6 hours to locate NOK and obtain authorization and medical and behavioral history. It may require an additional 1 to 2 hours to mobilize a postmortem recovery team and, if required, transport the donor. A given tissue recovery protocol may require an additional 1 to 6 hours to execute fully, thus creating an overall window of 5 to 12 hours from the time of donor death to completion of recovery.

Within the research recovery setting, one to four individuals usually prepare the donor and identify and excise organs and major structures for finer dissection. For additional processing, these organs and large samples can then be transferred aseptically to a second group of two individuals typically working on a back table or side tables within the operating suite or morgue. The second team uses finer dissection methods using a clean scalpel on a Teflon® cutting board designed for pathology specimens. This second team may subdivide larger samples into appropriate sizes, package them into biospecimen containers, track the identifiers on the biospecimen containers and their contents, and preserve the samples (usually in liquid nitrogen and/or formalin). It is helpful to designate one person at this station as a record keeper to track biospecimen container identification numbers, tissue types, and times of preservation. This division of labor is more efficient than tasking one individual with both dissection and record keeping. Under certain circumstances (and with limited staff), a dictation system with an electronic voice recorder can be used by the individual preparing biospecimens. This recording can later be transcribed.

It is often helpful to use laminated and liquid-resistant reference documents and diagrams in the postmortem research tissue recovery setting. These laminated documents can be cleaned, disinfected, and reused as reference sheets for lists of tissue samples to collect or as visual aids for gross or fine dissection techniques.

3. Description of Involved Staff

Transplant tissue recovery staff members are usually not pathologists and surgeons. They are skilled in tissue excision but not necessarily in other processes necessary to preserve tissues for research. The AATB offers a program of certification for TRO personnel. The CTBS examination tests candidates on their knowledge in all areas of tissue banking for transplantation, including donor and tissue suitability determination, tissue recovery, tissue processing, decontamination techniques, QC and product testing, labeling, record keeping, and clinical application of allografts. The examination is based on AATB standards and procedures.

In the academic research setting, a postmortem tissue recovery (autopsy) is most commonly performed with a pathologist in attendance. In the TRO setting, this function is frequently carried out by a CTBS technician who has received additional specialized training in research sample recovery.

CTBS technicians specialize in recovering bone, soft tissues, skin, and eyes/corneas for transplant. However, in the absence of specialized training, CTBS technicians may not have adequate gross pathology skills to identify, excise, handle, and dissect other anatomic structures frequently required for research. In these circumstances, it is helpful to ensure that CTBS technicians receive appropriate training (optimally provided by a pathologist or other expert) to successfully execute the research tissue collection protocols. One option to make this pathology expertise more widely available to TROs

within the postmortem research tissue recovery setting is through the involvement of pathology assistants. These individuals receive specialized training in anatomy, gross pathology, postmortem and surgical dissection, and sample preparation.

Training (and routine re-training) of onsite staff is the single most important investment that will maintain and improve specimen quality. Training for research tissue recovery (including demonstrations of anatomical dissections and sample processing) can be coordinated in a classroom setting using deceased donor organs and tissues. The more complex the research requirements, the greater the need to train recovery staff to the appropriate standards. A list of recovery team staff is provided in appendix J.

4. Health and Safety

Tissue recovery from postmortem donors should always include appropriate safety considerations and the standard use of universal precautions as established by the CDC.³⁴ A list of other health and safety considerations is provided in appendix K.

5. Program Quality Assurance

Postmortem tissue recovery organizations follow cGTP⁹ in accordance with FDA regulation 21 CFR 1271.145. Many of these requirements carry over into research tissue processes since the quality structure is already established at OPOs and TROs. TROs must have documented quality assurance (QA) and QC systems, including a quality reporting structure with defined responsibilities, published SOPs, formal training requirements, audit programs, preventive and corrective action systems, document control systems, facility management, environmental control, processing and process controls, process validations, labeling controls, and monitoring capability.

E. Bioinformatics for Postmortem Recovery

Tissue and organ recovery organizations may use various electronic data management systems to manage information associated with donor referrals, donor screening, medical history, and tissue recovery information. Many tissue recovery organizations also rely on hard-copy documentation to collect information in the field. However, bioinformatics tools will be most effective (and therefore most useful) when they are integrated into postmortem tissue recovery SOPs and protocols. Several recent publications provide examples of integrated informatics portals and workflows to support postmortem brain tissue recovery for research.^{35, 36}

1. Sources of Data and Documentation

Collection and management of donor biospecimen information should aim to be as comprehensive as possible to promote due diligence in donor screening and recruitment and to support QC. Optimally, conducting a complete antemortem and postmortem

physical assessment along with a social and family history questionnaire may facilitate more fully annotated specimens, but this is rarely feasible.

The following types of data are recommended when developing case report forms (CRFs) to support postmortem research:

- Donor demographics and behavioral history
- Serology and infectious disease status
- Medical history
- Laboratory and pathology data
- Antemortem medical conditions
- Postmortem donor management information
- Biospecimen collection, processing, and storage information

OPOs and TROs collect detailed data from the terminal event to the procurement of specimens. Moreover, the behavioral history required by the FDA is packaged in a standard template that enables additional questions to be added in cases of specific disease. TROs and rapid autopsy programs do not manage the patient as an organ donor, resulting in the collection of less organ-specific data (although demographics, time of death, and so forth are recorded). Both organ and tissue donors may be subject to resuscitative events such as fluid administration or cardiopulmonary resuscitation.

The TROs obtain the medical data via medical forms that are placed in a representative medical chart. Relevant data (e.g., demographics, patient consent information and documentation) are stored in a database. The most readily available clinical data will come from the tissue source, whether that be an institutionally sponsored rapid autopsy program, a TRO (e.g., hospital, morgue), or an OPO, with the caveat that there may be some overlap between TROs and OPOs.

Information collected in the postmortem tissue and organ recovery setting can be organized within three categories: (1) Information that is always gathered (e.g., patient age, sex, and known HIV or hepatitis status), (2) information that is usually gathered (e.g., past medical history and known illnesses), and (3) information that is rarely gathered; (e.g., menstrual and obstetric history or specific biomarker testing results). If the patient is enrolled in a clinical trial, the trial chart should provide a majority of the medical information that may include inpatient and outpatient information. If the patient is enrolled in a clinical trial that includes a survey, some behavioral history information (e.g., detailed smoking and alcohol use histories) may also be available.

All postmortem tissue recovery staff operating in the field are accustomed to collecting data in hard-copy CRFs. Remote electronic data entry may not always be feasible or available and should always be backed up by hard-copy CRFs.

Appendix I summarizes potential data for postmortem research biospecimen recovery.

2. Data To Contribute to the Development of Evidence-Based Standard Operating Procedures

By communicating the results of biospecimen research to the scientific and medical communities, researchers can significantly improve the quality of biospecimens collected in the future. Standardized data collection methods for postmortem research tissues can support these discovery efforts in biospecimen science and contribute to the development of evidence-based SOPs for the collection, processing, storage, and analysis of biospecimens. One standard that can be followed to help standardize data formats and facilitate data exchange has been established by the NCI Cancer Biomedical Informatics Grid (caBIGTM).

F. Ethical and Regulatory Best Practices

Ethical and regulatory best practices relevant to postmortem research tissue recovery encompass issues relating to donor family consent, ethical procurement and use of postmortem tissue, and regulatory oversight of the entire process. Ethical and regulatory best practices should aim to ensure that if the deceased individual made an anatomical gift during his/her lifetime, then the individual's wishes are honored and carried out, and in those instances in which the deceased individual did not make an anatomical gift, to confirm that consent given by the NOK is reasonable in scope, appropriately designed, and carried out to ensure the dignity of the postmortem donation.

It is equally important to ensure that consent issues are handled by trained personnel, from the time of initial approach of the donor family throughout the postmortem research biospecimen life cycle. Planning considerations include determining early in the process whether the donor made an anatomical gift and, if so, whether the gift was limited in any way. In the event that the donor's gift may be limited, there is the option to approach the NOK and request that he/she authorize the donation of additional organs and/or tissue for broader purposes.

1. Types and Content of Authorization and Consent for Postmortem Research Tissue Donation

Antemortem consent given by the donor and postmortem authorization given by the deceased donor's NOK are the standard forms of consent obtained for postmortem research tissue donation. Title 45 of the Code of Federal Regulations (45 CFR part 46) from the US Department of Health and Human Services regarding the protection of human subjects does not legally require that consent be obtained from deceased individuals.³⁷ It is, however, the recommended best practice to obtain the donor's antemortem consent when possible or the NOK authorization for donation. The informed consent should meet all federal, state, and institutional requirements. Three additional items specific to postmortem recovery should also be included in the consent:

- An indication of whether disfigurement to the body potentially will occur;

- A description of what the postmortem tissue recovery or rapid autopsy process will involve; and
- The length of time that the postmortem recovery or rapid autopsy will require and when the body will be returned to the family.

2. Determination of Authorization Versus Informed Consent

Who can make an anatomical gift, how, and for what purposes are questions of state law. While the law varies among states, it is generally the case that any competent adult can make an anatomical gift of his/her organs and tissues before death. The gift takes effect upon the individual's death. If the decedent did not make a gift, the reasonably available NOK (as defined by state law) can authorize donation postmortem. Most state jurisdictions (38 out of 51) have now adopted the Revised Uniform Anatomical Gift Act of 2006 (RUAGA), which mandates that the deceased individual's wishes to donate/refuse to donate must be respected and that if the deceased individual made a gift (or refused), no other person may revoke or amend that gift. The NOK, however, may agree to make a gift that is not contrary to the donor's wishes; e.g., if the donor agreed to donate only for transplant and therapy purposes, the NOK may agree to donate for research and education. Of the remaining state jurisdictions, all but Vermont are listed by UNOS as observing first-person consent (for additional details, see UNOS Donor Designation [First Person Consent] Status by State³⁸).

An individual may also authorize donation by a "document of gift." The gift is accomplished most commonly by designation on a driver's license or by registering with an online donor registry. OPOs and TROs include this document in their case record as the authorization form. In most instances when the individual has made a gift, the recovery agency will typically contact the legal NOK to advise him/her of the donation and obtain additional medical and behavioral information. The agency may also request additional authorization, such as use for research, if the donor's gift did not encompass the purposes for which the gift could be used.

3. Practical Considerations Related to Authorization/Consent

Institutions should aim to implement a formal authorization process that specifically addresses issues related to donor recruitment, biospecimen recovery, and research utilization of postmortem biospecimens. This process should provide for unspecified research use (sometimes referred to as a "biobanking" use) of biospecimens and implement informed authorization for all living patients and the NOK of deceased donors.

Living patients seeking to donate should make their wishes known in writing and share these wishes with their significant others and/or family. Generally, at the time of death the family will be approached to help facilitate the decedent's known wishes and to provide information regarding medical and behavioral history. If a patient does not have a prior documented donation decision, the NOK will be approached to make a donation

decision on behalf of the decedent. In situations in which consent is granted, the body must arrive from the morgue with an autopsy consent form signed by the patient's NOK, a potential logistical hurdle depending on whether the body comes from a medical institution or from another setting.³⁹ OPOs are able to obtain recorded and telephonic consent from the NOK to authorize donation for all lawful purposes; i.e., transplant, therapy, research, and education. Although such a practice can be beneficial for research donation, logistical issues still must be overcome.

The following issues are particularly relevant to the consent process for postmortem research tissue donation for biobanking use and for studies that involve genomic analyses:

- Risk of loss of privacy and confidentiality
- Future unspecified research use
- Extensive genomic and other molecular characterization of tissues that may have privacy and confidentiality implications for NOK
- Treatment of some tissues and cells such that they will be maintained in a laboratory for an extended time
- Potentially collecting a much larger quantity of tissue than in a typical autopsy.

Each of these issues, and the associated risks, must be clearly addressed during the consent/assent process.

4. Protocols for Authorization/Consent

It is recommended that the request for an anatomical gift for research purposes be made by individuals who are trained donation requesters who, in appropriate cases, have received additional training in patient-oriented research and donor privacy and confidentiality practice. The donation should be documented in the manner prescribed by law for postmortem anatomical gifts and filed appropriately. The approach used to authorize tissue donation varies by program. For example, rapid autopsy programs consent in person (either antemortem or with NOK), while OPOs and TROs usually authorize donations via telephone, at which time the discussion and donation authorization from the legal NOK are recorded. These discussions may be conducted by staff employed directly by the OPO, TRO, or outsourced and contracted to specialized call centers. Prior to proceeding with any type of recovery, the tissue recovery coordinators or TROs confirm authorization for research during their initial screening of the donor chart and review any recovery restrictions indicated by the family or the ME/coroner. These coordinators have the capacity to include additional "checkpoints" as necessary and directed by a specific research recovery protocol.

To avoid the perception and/or risk of duress, all individuals involved in determining death should be excluded from the consent process of the NOK antemortem and postmortem. In most jurisdictions, State law prohibits the physician who attends the decedent at the time of death from participating in the removal or transplantation of tissue

from the decedent. The physician may be involved in introducing the OPO or TRO staff or introducing the donation discussion. The decision to request such involvement, however, should be made by the recovery organization in consultation with hospital staff and in accordance with agreed-upon recovery protocols. While the composition of consent forms varies due to State requirements and local and organizational constraints, templates are recommended to promote standardization.

TROs that recover postmortem biospecimens should obtain consent and/or authorization prior to recovering tissue for research. All authorization forms use similar methods to describe the donation process. In January 2004, the AOPO, the AATB, and the Eye Bank Association of America jointly published Model Elements of Informed Consent.⁴⁰ In addition, many TROs collect the name of the person who accepted the donation, specific disclaimers, funeral wishes/arrangement information, specific choices regarding consent for transplant, and consent for medical education and research.

The donor NOK may at a future date choose to withdraw consent for use of tissues in research. This withdrawal of consent can be implemented when the NOK notifies the biorepository director of the request. Any remaining tissue in the biorepository from the specified donor is then removed and destroyed. Tissue samples that have already been distributed or used cannot be retrieved. Data associated with the donor may or may not also be withdrawn, depending on the policies of the specific biorepository. If the data are removed, all copies held at the OPO or TRO in electronic backup files and all paper files are destroyed.

5. Ethical Review and Regulatory Considerations

Ethics review may vary by institution. In the United States, Federal regulations define human subjects as living human beings; thus, the legal requirement that all human research undergo IRB review does not extend to research with the deceased (see 45 CFR Part 46).³⁷ The Consensus Panel on Research with the Recently Dead, however, recommends review by a multidisciplinary panel to address the distinctive ethical issues involved.⁷ Best practices suggest that postmortem tissue collection should receive formal ethics review to ensure that it is properly conducted and the tissues and data used appropriately. It is recommended that all institutions organize and convene, as needed, a specialized Committee for Research Involving the Dead (CORID) that is regularly integrated with full IRB regulatory review for all rapid autopsy programs and protocols.

While not legally required, it is recommended that such a committee approve all protocols involving research tissue collection and that the committee certify that ethical concerns have been addressed.^{41, 42} With regard to an institutional program, the local Office of Human Research should also be consulted if the rapid autopsy program is performed in conjunction with a clinical trial. If the rapid autopsy program is part of a cancer clinical trial, IRB review should aim to be performed in tandem with review from the institution's clinical trial and data safety monitoring committee. In other countries

such as Canada, research with human remains including cadavers requires research ethics board review and approval.⁷

TROs are regulated by the FDA under 21 CFR. OPOs are federally designated by CMS and inspected and recertified on a 4-year cycle. Since they recover tissue for research from deceased donors, OPOs typically have an internal committee review process and do not usually submit research tissue collection protocols to the FDA or to large institutional IRBs or central IRBs. Obtaining formal representations of ethical committee (IRB) approval (outside of academic institutions) is not routine for OPOs and TROs although generally all have some type of internal review process that is conducted to determine which protocols and research projects will be supported.

G. Legal Considerations

1. Introduction

This description highlights aspects of the system governing organ procurement and distribution as it operates presently, including relevant organ transplant laws and policies and their impact on the process of obtaining postmortem non-transplantable organs and tissues for research.

2. Common Law: The Law of Informed Consent

a. Medical Treatment

Informed consent is the initial and critical legal requirement for donated organs or tissue to be made available for any use. The right to consent to medical procedures is reflected in Justice Benjamin Cardozo's observation that "every human being of adult years and sound mind has a right to determine what shall be done with his own body."⁴³ This principle reverberates through case law as well as through a variety of Federal and State laws, regulations, licensure and accreditation standards, and oft-cited underlying non-legal treatises such as the Nuremberg Code, Belmont Report, Declaration of Helsinki, and policies of the National Bioethics Advisory Commission, the American Medical Association, and various academic institutions.

b. Organ Donation

State law determines who can make an anatomical gift, how this gift is made, and what purposes the donation may serve. Historically, State law pertaining to organ and tissue donation is based on the UAGA, first issued in 1968 by the National Conference of Commissioners on Uniform State Law. The UAGA provided that either the donor or the donor's NOK must "opt in" to the organ donation system and consent to organ donation and created the power, not yet recognized as common law, to donate organs, eyes, and tissue in an immediate gift to a known donee or to any donee who may require an organ to survive. The UAGA also created a hierarchy of

decision-makers (the NOK) who may elect to donate organs or tissues and opt in on behalf of the deceased if the deceased did not make his/her wishes known. The UAGA also provided immunity from civil and criminal proceedings for those who act in good faith in accordance with the terms of the Act or the anatomical gift laws of another State. The UAGA was adopted in all 50 States and the District of Columbia.

The UAGA was revised in 1987 and again in the 2006 RUAGA. The RUAGA strengthened the rights of the donor. It mandates that the donor's decision, when made in the manner prescribed by the RUAGA, must be honored, and it expressly forbids anyone else from amending or revoking a gift made by the donor. The RUAGA has been adopted in 38 jurisdictions, and with the exception of Vermont (where the RUAGA is currently under consideration by the State legislature), all remaining jurisdictions have espoused first-person consent.

c. Liability When Informed Consent Is Lacking

Possibly the most famous case involving the failure to obtain informed consent in connection with organ and tissue donation is the case of *Moore v. the Regents of the University of California*.⁴⁴ In this case, plaintiff John Moore sued his doctor for the conversion (a common law misappropriation claim) of his spleen, which had been removed for therapeutic purposes. The doctor later used the spleen to develop a patented and profitable cell line. Although the court sided against the plaintiff on his conversion claims, it found the concept of informed consent sufficiently broad to encompass occasions when a provider has a personal, financial interest in the procedure at hand. The Moore case underscores the importance of obtaining informed consent to remove tissue for uses other than in connection with the patient's own treatment.

Other common law claims that have been generally unsuccessful but are continually made are claims of a property right in organs or tissues that was somehow violated (or property misappropriated) in connection with organ or tissue removal and use. The Moore case and its rejection of the conversion claim is the most frequently cited example of this type of case. In declining the claim for conversion, the court held that the patented fruit of research resulting from excised tissue is factually and legally distinct from the excised tissue.

It is worth briefly noting that legal issues affecting the research use of human tissues in academia, Government, and industry in the United States extend abroad. Many governments are struggling to reconcile existing law and policy with new technologies that make use of donated human tissue.

3. Federal Law

a. National Organ Transplant Act (NOTA)⁸

The NOTA was passed in 1984 to address the Nation's critical organ donation shortage and improve the organ matching and placement process. The Act established the OPTN to maintain a national registry for organ matching by a private, nonprofit organization (UNOS) under contract with the U.S. Department of Health and Human Services. Every patient who awaits a transplant in the United States is registered in the UNOS data network, and all have equal access to donated organs.

A significant function of NOTA is to prohibit the commodification of organs and tissue. Specifically, NOTA made it illegal for any person to “knowingly acquire, receive, or otherwise transfer any human organ (broadly defined to include donated tissue) for valuable consideration for use in human transplantation if the transfer affects interstate commerce.”⁴⁵ In this context, “valuable consideration” does not include reasonable payments associated with the removal, transportation, implantation, processing, preservation, QC, and storage of a human organ or costs to a donor in connection with donation.⁴⁶ This exclusion is the only way that an OPO, transplant program, or other participant in the procurement process can receive compensation for efforts.

b. Participation for Hospitals

The Omnibus Budget Reconciliation Act of 1986 (OBRA) requires all hospitals that participate in Medicare or Medicaid to institute a “required request” policy. Specifically, hospitals must develop and maintain written policies and procedures for identifying potential donors, providing families with the opportunity to donate organs and tissue as well as with a right to decline. OBRA also requires hospitals to affiliate with their regional OPO.

As a condition of participating in Federal healthcare programs, CMS has established Conditions of Participation that require hospitals to notify their regional OPO of every death or imminent death, including any patient who has been placed on a ventilator due to severe brain injury, so that the OPO can make a determination on medical suitability for transplant. CMS recognizes that donor families have the right to make anatomical gifts if the donor has not previously declared his/her anatomical gift wishes. In particular, it requires the OPO to provide to the individual(s) responsible for making the donation decision, at a minimum, the following:

1. A list of the organs and/or tissues that may be recovered;
2. The most likely uses for the donated organs or tissues;
3. A description of the screening and recovery processes;

4. Information about the organizations that will recover, process, and distribute the tissue;
5. Information regarding access to and release of the donor's medical records;
6. An explanation of the impact the donation process will have on burial arrangements and the appearance of the donor's body;
7. Contact information for individual(s) with questions or concerns; and
8. A copy of the signed consent form if a donation is made.

If an OPO does not request consent to donate because a potential donor consented to donation before his/her death in a manner that satisfied applicable State law requirements in the potential donor's State of residence, the OPO must provide information about the donation to the family of the potential donor, as requested.

4. State Law and Efforts To Increase the Supply of Organs for Transplant

a. Donor Registry Laws

A recent legislative development at the state level is the implementation of donor registries to increase organ donations. Donor registries are established in conjunction with state registries of motor vehicles and provide OPOs with the ability to access the registry's database of those who have indicated consent to become organ donors on their driver's license. Once the OPO has confirmed that the donor has consented through the donor registry, the OPO will no longer obtain NOK consent for donation. The OPO will continue, however, to provide donor families with information, support, and aftercare services.

b. Laws Governing Informed Consent

As critical as the informed consent requirement is, no state or federal law has established clear legal or ethical standards for the minimum amount of information necessary for a decision to donate to be an informed one (see 45 CFR Part 46).³⁷ Instead, state actions have focused on the method by which the public is informed about the donation process and standards surrounding signing donor documentation; i.e., in the presence of a notary public.

5. Contract Law

a. Informed Consent Documents

An informed consent document functions as a contract and memorializes the understanding between an institution and patient (or NOK in the case of postmortem tissue recovery) as to the scope of the medical procedures that will be conducted. Often, institutional informed consent documents include provisions indicating a patient's agreement to allow excised tissue (e.g., blood, biopsy, fluid) to be used for

research or educational purposes. Such excised tissues have tremendous value, not only in connection with research and education but also increasingly for commercial use. A carefully drafted informed consent document and process serve as the legal basis for the institution to use tissue and associated clinical information gathered from patients for purposes other than the patient's own treatment.

b. Contracts Between Institutions

Researchers at different institutions regularly make tissue and other biological materials available to each other via contract or, more specifically, via a materials transfer agreement (MTA). MTAs are short agreements that specify the purpose for which the tissue will be used, prohibit use of tissue *in vivo*, and ensure compliance with NOTA, specifying that any compensation exchanged between the institutions is for reimbursement of expenses associated with providing the material and not for the purchase of the materials. If the institutions are exchanging proprietary materials, the MTA will contain language delineating ownership rights to new uses, modifications, derivatives, or progeny.

c. Contracts Between OPOs and Institutions

Hospitals are required by Federal law to contract with their regional OPOs. In addition to reflecting the requirements of Federal law, OPO contracts reflect the policies of the particular OPO. Through the contracting process, the OPOs are able, to an extent, to dictate hospital policy in connection with organ donation.

d. Contracts Between OPOs and Other Entities

OPOs also enter into agreements with other (typically nonprofit) organizations in connection with TROs to distribute tissue for non-transplant purposes and providing organs and tissues for research uses. These agreements must be consistent with Federal law; for example, they may not contravene NOTA's prohibition on remuneration in connection with organ or tissue transfer. Biorepository facilities may contract with these entities as well to obtain organs or tissues that are suitable for research use.

6. The Impact of Policies on the Law and the Flow of Organs and Tissues

The policies of various organizations and entities involved in the organ transplant process control the flow of organs and tissues. UNOS policies, for example, aim to constantly increase the supply of organs or tissues available for transplant. They also dictate federal laws with respect to organ/tissue transplant. Similarly, OPOs develop policies with the goal of increasing transplantation. These policies must be consistent with federal law although they may vary throughout the country and reflect different approaches among OPOs.

Federal policies on biological materials transfer were established to standardize and encourage the sharing of biological materials while preventing overreaching MTAs aimed at siphoning the intellectual property of the transferring institution. Federal biological materials transfer policies are consistent with NOTA in that they prohibit remuneration in exchange for biological materials.

Finally, institutional policies, whether formal or informal, bear on the flow of organs and tissues and address such issues as the content of an informed consent document, interaction with organ or tissue donors and/or their families, the use of organs or tissue for research, and the use or transfer of tissue for commercial applications.

H. Business Considerations

1. Acceptable Revenue Streams and Distribution Channels

The biotechnology and pharmaceutical industries are interested in accessing human postmortem tissues for use in therapeutics research and development programs. Biospecimen access and quality significantly impact the ability, time, and expense of bringing therapeutics through the drug development process to the marketplace. For-profit companies may be particularly interested in contributing to the development of a postmortem tissue acquisition resource that could lower their development costs, contribute to the success of therapeutic products, and decrease the time required to bring those products to market. Issues regarding the cost and commercialization of human tissue samples appear frequently with regard to tissue procurement activities. Many organizations address these issues by defining a policy of “not selling” tissues, instead charging on a fee-for-service basis or transferring tissues under a licensing agreement.

2. Common Service Models—Costs, Pricing, and Reimbursement

The postmortem sourcing model employed will significantly impact the cost of goods and services, and a variety of cost elements factor into the sourcing cost of collecting high-quality postmortem biospecimens for research. Most sourcing organizations share common cost components such as staff, training, project management, supplies, transportation, hospital fees, and data collection. There may be differences, however, in the relative distribution of these costs associated with the type of sourcing organization, their respective standards of practice, overhead structure, and tissue recovery methodology, among others. The particular research project requirements for biospecimens as they relate to quality, tissue types and quantities, processing needs, and dataset requirements must also be factored into sourcing costs.

When working with OPOs, for example, research tissues can be recovered in conjunction with organ recovery for transplant. The tissue recovery cost associated with this “piggy-back” approach may be less than if the recovery is from research-only donors. In general, postmortem research tissue recovery tends to be more laborious—and therefore more costly--than surgical tissue recovery due to the requirement to recover biospecimens from

many different organ/tissue types and the high volume of samples that can be recovered and must be processed.

Transplant organ recovery is carried out in aseptic conditions in a medical center operating room. Following such transplant recoveries, it tends to be costly to recover additional biospecimens for research from the operating room theater due to the additional reimbursement required for the time used in this high-value service space. Therefore, postmortem research biospecimens can be collected after recovery of transplant organs when the operating room interval has passed and medical staff and surgeons are no longer needed. Once permission has been given for research tissue recovery in the operating room, the OPO pays for the additional operating room time and associated testing procedures, as necessary. In some cases, such as kidney donation, Medicare regulates the prices that an OPO can charge. The costs related to the placement of a transplant organ are covered by the organ recipient's health insurance. In contrast, for research tissue recovery, the OPO charges the recipient TRO or end user a fee for the recovery services. Reimbursement to OPOs is governed by CMS payment rules. These payment regulations should be discussed with the OPO prior to any partnership agreement to ensure transparency and that policies are followed and reimbursement expectations are articulated and understood.

If partnering with a rapid autopsy program at a medical center, costs accrue in association with use of the morgue, associated staff, and other resources, such as the pathology staff, supplies, and data collection. Depending on the structure of the program, there may also be costs associated with donor recruitment and for obtaining consent for postmortem tissue donation for research.

When considering partnerships with sourcing organizations, it is important to recognize their standards of practice regarding adoption and implementation of best practices, availability of experts in decedent affairs/family discussion/informed consent, donor recruitment, and access to appropriate recovery facilities and resources. Organizations should have information technology and electronic medical record systems that will allow access to donor clinical data. If data are stored in a paper-based system, access for biospecimen annotation purposes should be made available following appropriate policy and confidentiality requirements. Sourcing organizations should also have qualified and trained staff, supplies, and facilities to ensure success with biospecimen recovery and collection of clinical data. It is also important to establish expectations concerning the donor family's responsibility for covering costs associated with transportation of the donor's body following tissue recovery, body preparation, and funeral costs.

Organizations that may be suitable for postmortem biospecimen collection include OPOs, TROs, academic or community medical centers, and ME offices. In addition, third-party tissue brokers, such as the National Disease Research Interchange and International Institute for the Advancement of Medicine, work with OPOs and TROs to redirect human tissue samples for use in research. When considering partnering, due diligence should also include ensuring that sourcing organizations and the chain of resources that they may

utilize are current with all standard and customary accreditations and licensures required for their business activities.

The following concepts should be kept in mind when considering establishing cooperative working relationships with sourcing organizations for the recovery of postmortem research tissues:

- Multiple sourcing providers should be considered for partnering.
- Training will be essential for quality operations.
- Reasonable resource, operating, financial, and workload expectations should be outlined and maintained by all parties.
- Partners must be willing and able to implement and consistently follow provided SOPs and QA standards.

3. MTA Guidance

An MTA or letter agreement MTA is a contract that governs the transfer of tangible research materials among academic, Government, and commercial organizations when the recipient intends to use it for his or her own research purposes. The MTA defines the rights of the provider and the recipient with respect to the materials and any derivatives. MTAs are important because they specify the rights, obligations, and restrictions of the providing and receiving parties with respect to issues such as the following:

- Ownership of materials and modifications or derivatives of the materials made by the recipient;
- Limits on the recipient's use of the materials and related liability;
- Restrictions on the recipient's ability to transfer the material, modifications, and derivatives to third parties;
- Rights to inventions resulting from the use of the materials;
- Rights to publish research obtained through the use of the materials; and
- Reporting and confidentiality obligations.

It is recommended that all tissue processing parties that release or obtain tissue or biospecimens for research require and execute a mutually agreed-upon MTA. The MTA should be executed and approved by the appropriate institutional authorities prior to the release of biospecimens and associated clinical data. Developing and executing an MTA may be a lengthy process; therefore, MTAs should be initiated early in the study planning timeline to allow sufficient time for negotiation of terms and legal review. It is also advantageous to have an MTA template that incorporates a set of fundamental terms and standard structure, as outlined below.

As part of an effort to improve access to research tools and materials, the NIH has strongly recommended that scientists at nonprofit institutions use a Simple Letter Agreement MTA when exchanging materials. In general, MTAs will address the

following issues, among others, to articulate a clear understanding of requirements, terms, and obligations associated with the transfer and use of biospecimen material:

- **Definition of material:** Biospecimen material is defined as including both the physical biospecimens and the associated annotation data.
- **Use limits:** Biospecimen material is for research and development use only and not to be used directly in humans for treatment, transplant, or donor diagnosis. Final disposition of the biospecimen materials and their derivatives will be determined by the recipient of samples.
- **Transfer to other parties:** The recipient of samples shall not transfer or sell biospecimens and their derivatives to any other parties for any purposes. The recipient will direct all such inquiries to the sponsoring organization for review.
- **Compliance:** All parties must comply with relevant laws.
- **Intellectual property:** The biospecimen provider does not retain any intellectual property reach-through rights to datasets generated from biospecimens, derivatives, or to future discoveries and products arising from those datasets.
- **End users:** MTA terms will not differentiate between nonprofit and for-profit organizations, data-generating networks, or use for product research and development.
- **Confidentiality:** The provider will warrant that data comply with the HIPAA-defined “Limited Data Set” with the expectation that date/time stamp and geographical data will be included. The recipient will not attempt to identify or contact the biospecimen donor family members directly.
- **Source acknowledgement:** In all oral presentations or written publications concerning the research project, the recipient will acknowledge the provider’s contribution of this biospecimen material.
- **Reimbursement:** The recipient will provide compensation to the provider according to a defined fee schedule to cover costs associated with acquisition, processing, handling, and annotating the research material.
- **Safety:** The recipient will ensure training of staff and use of appropriate universal precautions to minimize any health risk associated with using human biospecimen materials in research.

A sample Simple Letter Agreement MTA and a more complex MTA are provided in appendix L. Additional information about MTAs is available in the NIH’s *Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and*

*Disseminating Biomedical Research Resources*⁴⁷ and the Council on Government Relations' "Materials Transfer in Academia."⁴⁸

I. Donor Family and Community Considerations

1. Guidelines for Donor Families

After each donation is received, the recovery organization should offer the donor's family gratitude and sympathy, bereavement resources, and information about some of the research programs that may use the tissue. The use of respectful language by all recovery organizations is essential as recommended by donor families through work with national donation organizations (appendix M). Generally, tissue recovery organizations should adhere to the procedures outlined below.

Within 30 days of receiving a donation, the biospecimen recovery organization will send a packet of information to each donor family that must include, but not be limited to, inserts on the following topics:

- A sympathy note or letter thanking the donor and his/her family for the gift of tissue. This letter should detail in simple terms the specifics of how the tissue might be used in various research projects (appendix N).
- A brochure from the biospecimen recovery agency.
- The Donor Family Bill of Rights (appendix O).
- A separate letter from the biospecimen recovery organization's finance office indicating that there is no cost to the family or estate for donation to research (appendix P). This letter should indicate that the donor family is responsible only for standard funeral/mortuary or cremation expenses or an official autopsy, if requested, for diagnosis or to determine cause of death. It should also indicate whom to contact at the recovery agency should there be any charges related to the donation.
- A list of national bereavement resources (appendix Q).

Most organizations that conduct research using donated tissue specimens have a policy of not returning research results to the donor and/or his/her NOK. This practice reflects several complex factors, including the difficulty of parsing out data specific to any one sample and donor; the fact that one sample does not usually produce data that are significant in the absence of data from the rest of the experimental cohort; the inability to collect donor-specific data from individual researchers in Government, academia, or industry; and the issue of appropriately interpreting and understanding the data. As part of the informed consent process, a policy statement is generally provided that addresses the inability to return data.

2. Guidelines for Community Relations and Addressing the Public

Public perceptions of organ and tissue donation can be best influenced through public education and media campaigns (e.g., public relations efforts, advertising and marketing campaigns), with the primary goal of conveying the importance of signing up to be a donor. National efforts have shown that the more the public knows and understands the need for donors, the higher the rates of donor designation. Higher donor designations promote higher authorization rates for organ and tissue donation for transplantation, research, education, and therapy.

a. Communication With Advocacy Groups

It should be the policy of the biospecimen recovery agency to cooperate fully with all recovery agencies that work within the services area. This cooperation will include, but not be limited to, the following:

- Using the same or parallel messaging in educational and media materials
- Using a variety of established materials, best practices, initiatives, and campaigns to educate the public
- Participating with local and national advocacy groups to develop programs (task forces/speaker networks/support groups) that spread awareness about new developments in tissue for research (groups include, but are not limited to, Donate Life America, AATB and its members, AOPO and its members, Health Resources and Services Administration, and the Organ Donation and Transplantation Alliance)
- Developing and sharing a list of donor family speakers who have donated for research and are able to share the emotional impact of that decision.

b. Public Perceptions and Media Coverage

A worthy public education message of the biospecimen recovery agency is that donated organs and tissues for medical research may result in cures for deadly diseases that will, in many cases, prevent transplantations currently required to treat certain conditions. Thus, medical research will decrease morbidities and vastly improve the quality of life for millions of people.

It should be the policy of the biospecimen recovery agency to be transparent regarding requests from the public and the media. Continuing misperceptions about donation, recovery, and research greatly influence public understanding of these areas. The biospecimen recovery agency is required to have a clear and easily understood authorization form. There must never be any misunderstanding by a donor family about what is being requested for donation and that it may be used for research.

The crisis of organ shortages in the United States helps to drive most local and national public education and media campaigns. Eighteen people in the United States die every day due to the lack of organs available for transplant. Every 11 minutes,

another name is added to the list of individuals who need a transplant. Figures such as these can be used as a means to appeal to an individual's altruism, and generosity helps support the case for asking citizens to make the decision to donate for transplantation, research, education, or therapy.

c. Religious and Cultural Views on Organ Donation and Transplantation

Most religious traditions and cultural views support organ and tissue donation as a charitable act of love and giving. Appendix R, a document adapted from OrganDonor.gov and the Wisconsin Donor Network's *Organ and Tissue Donation: A Reference Guide for Clergy* (1995), provides brief descriptions of some of the views of various religions and cultures about organ and tissue donation specifically for transplantation. In some cases, these views can be interpreted to include research use.

J. Conclusions

The recommendations and operational tenets outlined in this document provide a comprehensive programmatic approach for establishing a postmortem biospecimen recovery program. Although logistically complex and operationally demanding, postmortem research tissues can be an important accessory source of biospecimens suitable for a broad array of research applications to support scientific and clinical discovery. Understanding the broad elements of these best practices for postmortem tissue recovery can serve as a foundation on which to further customize donor selection and operational criteria to meet the needs of specific research projects. Furthermore, awareness of these best practices can foster more effective collaborations, mitigate potential logistical challenges, and ultimately generate value from the dual goals of promoting postmortem research tissue donation options for families and meeting the ongoing needs of researchers.

Partnering with academic rapid autopsy programs, OPOs, or TROs can be part of a successful strategy for postmortem research tissue recovery. As such, it is important to actively seek lessons learned from other postmortem programs to ensure that any newly established postmortem tissue recovery program is appropriately designed and resourced to be successful and meet the rigorous demands of modern research. With proper program design, appropriate resources, willing and skilled sourcing partners, and strong project management, a postmortem tissue acquisition program can be a significant contributor to the research enterprise. Postmortem biospecimens can serve, in some instances, as surrogates for surgically acquired tissues from living donors in biospecimen research. With a proportionately higher potential yield in biospecimen quantities from a single donor than with surgical tissue recovery, postmortem tissues may help relieve some current constraints on biospecimen-based research and therefore have an important impact on the development of new diagnostics and therapeutics.

WEB RESOURCES

American Association of Tissue Banks (AATB; www.aatb.org)

American Board for Transplant Certification (ABTC; www.abtc.net)

Association of Organ Procurement Organizations (AOPO; www.aopo.org)

BrainNET – Europe (www.brainnet-europe.org)

Biospecimen Research Network (BRN; biospecimens.cancer.gov/researchnetwork/fo/brn.asp)

Eye Bank Association of America (EBAA; www.restoresight.org)

Health Resource and Services Administration Organ Procurement and Transplantation Network (HRSA OPTN; optn.transplant.hrsa.gov/)

International Air Transport Association (IATA; www.iata.org)

International Institute for the Advancement of Medicine (IIAM; www.iiam.org)

Musculoskeletal Transplant Foundation (MTF; www.mtf.org)

North American Transplant Coordinators Organization (NATCO; www.natco1.org)

National Center for Research Resources (NCRR; www.ncrr.nih.gov)

National Disease Research Interchange (NDRI; www.ndriresource.org)

National Eye Institute (NEI; www.nei.nih.gov)

National Institute of Allergy and Infectious Diseases (NIAID; www.niaid.nih.gov)

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS; www.niams.nih.gov)

National Institute of Child Health and Human Development (NICHD; www.nichd.nih.gov)

NICHD Brain and Tissue Bank for Developmental Disorders (www.btbank.org)

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK; www.niddk.nih.gov)

NIH Office of Rare Diseases Research (ORD; <http://rarediseases.info.nih.gov>)

NCI Office of Biorepositories and Biospecimen Research (OBBR;
<http://biospecimens.cancer.gov/default.asp>)

Occupational Safety and Health Administration (OSHA; www.osha.gov)

United Network for Organ Sharing (UNOS; www.unos.org)

RELEVANT STANDARDS

FDA Guidance on Donor Screening Criteria for Transplantable Tissues

AATB Good Tissue Practices

AOPO Accreditation and Standards

FDA Current Good Tissue Practices

CMS Regulations and Audits

NCI Best Practices for Biospecimen Resources

International Society for Biological and Environmental Repositories Best Practices

Collage of American Pathologists Guidelines

Department of Health and Human Services Guidelines

45 CFR 46

APPENDICES

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APPENDIX P—Sample Finance Letter to Donor Families

APPENDIX Q—Bereavement Resources

APPENDIX R—Religious and Cultural Views on Organ Donation and Transplantation

APPENDIX A

General Sequence of Events for Postmortem Research Tissue Recovery

(Ref: L. Miranda, 2009)

The following list describes the general chronology (sequence of events) related to postmortem biospecimen recovery.

1. Antemortem Stage

- Diagnosis
- Clinical treatment history
- Preconsent (some circumstances)

2. Postmortem Stage

- Donor death
- Death referral
- Donor screening/NOK interview
- NOK consent

a. Prerecovery Phase

- Dispatch of recovery teams
- Recovery preparation

b. Recovery Phase

- Organ recovery (OPO)
- Tissue recovery (TRO)
- Research tissue recovery
 - Organ and tissue excision
 - Biospecimen preparation (dissection, preservation, packing, and labeling)
 - Record keeping and biospecimen data tracking
 - Shipment of biospecimen to end user
 - Temporary local storage

c. Postrecovery Phase

- Final distribution
- Scientific analysis

APPENDIX B

Areas of Expertise for Postmortem Recovery of Tissue for Research

This list describes the key areas of expertise in which postmortem research tissue recovery partners should demonstrate proficiency.

1. Ability to establish and manage postmortem donation of organs and tissues for transplantation, research, and therapy.
2. IRB submissions and approvals, as applicable.
3. Donor screening and recruitment (including NOK informed consent/authorization and medical and behavioral interviews).
4. Onsite coordinator to ensure adherence to recovery protocol and collection of data.
5. Coordination of sufficient numbers of trained clinical and technical (full-time equivalent) personnel and facilities to enable the rapid deployment of resources to acquire large numbers of low-PMI tissues.
6. Staff training on the requirements to manage postmortem protocols.
7. Pathologist, PA, diener, or other appropriately trained individual who can direct the anatomical identification, excision, dissection, annotation, and preparation of the specimens to ensure collection of correct region/orientation of the sample.
8. Ability to collect tissues under FDA cGTP guidelines.⁹
9. Appropriate stabilization, suitable storage and shipment of obtained tissues, and transfer of associated clinical data, using best practices for sample collection, handling, fixation, and storage.
10. Quality biospecimen annotation that includes the capture of critical parameters for each tissue sample; e.g., PMI, collection, processing, and storage conditions.
11. Clinical and medical data collection (including obtaining adequate clinical and pathology data to accompany the acquired tissues) and data management to ensure donor confidentiality.
12. Available systems for short-term storage of frozen biospecimens with temperature monitoring and maintenance routines.
13. Availability of security, electrical power backup systems, and alarm systems for specimen storage.

14. Adherence to a total quality program that assesses, measures, and ensures that SOPs for tissue procurement from rapid autopsy and from organ donors are followed strictly and that high-quality, low-PMI tissues are obtained.
15. Ability to transport and ship all samples immediately to multiple destinations.
16. Potential rate of participant enrollment and biospecimen accrual.
17. Ability to address the full breadth of relevant ethical, legal, and policy issues, including permission for unspecified future use, compliance of collected samples and data with current laws and regulations, compliance of samples and data with current accepted best ethical practices, and contractual status under MTAs.
18. Clinical data quality, including the availability of electronic records and the ability to maintain contact with donor families or their records to capture longitudinal information.
19. Biological quality, including (when required) histomorphologic representativeness of the tissue, mass adequacy of individual samples, and molecular integrity.

APPENDIX C

Categories of Information That May Define Donor Inclusion Criteria

The following categories of information are useful for defining and communicating donor inclusion criteria for research studies that utilize normal postmortem biospecimens.

1. Donor Demographics

- Age
- Gender

2. Serology and Infectious Disease Status

(e.g., HIV, HBV, HCV, syphilis, HTLV I or HTLV II, CMV, TB)

3. Medical History

(confirming the absence of the following conditions if appropriate)

- Genetic syndromes or chromosomal abnormalities (e.g., Down syndrome)
- Primary cancer or metastatic cancer
- Chemotherapy treatment
- Radiation treatment
- Diabetes mellitus, type I or II
- Autoimmune disease
- Renal disease

4. Antemortem Medical Conditions

- Sepsis (widespread or localized)
- Period of ventilation (intubation)

5. Postmortem Donor Management Information

- Cause of death
- Temperature of donor body storage
- Recovery within X hours postmortem
- PMI for completion of research biospecimen recovery

APPENDIX D

Case Studies

The following case studies describe examples of normal postmortem research tissue collection projects, the intended project goals, methods of implementation, real-world outcomes, and useful lessons learned.

Case Study 1

Collection of Assorted Normal Control Postmortem Tissues for Research from a Healthy Donor

Background

A researcher from a biotechnology company has requested that a local TRO assist with the collection of assorted normal control tissues from five healthy donors. These tissue samples will serve as control biospecimens to test the cross-reactivity of novel biomarkers that have been developed to detect the presence of disease in tissue samples from living donors.

The researcher has requested that a set of 30 different tissues be collected from each of 5 normal donors who are free of all major chronic diseases. The researcher supplies a sample collection protocol to the TRO outlining the preferred donor screening criteria and technical specifications for biospecimen preparation. The researcher would like to obtain tissue samples from donors who are either male or female (preferably an equal mix) under the age of 50. The researcher has requested that each donor have no genetic syndrome disorders, chronic diseases, or any history of cancer. The researcher requests that the TRO collect 1.0-gram tissue samples snap-frozen in liquid nitrogen. To obtain high-quality RNA, the researcher requests that the PMI for recovery be no longer than 4 hours.

The researcher has the expectation to acquire all samples within 3 months. The TRO indicates that with the given parameters, fulfillment of the request may take longer than expected unless some criteria change. Both parties agree to begin screening potential donors to assess their prevalence under the given criteria.

Research Donor Screening Progress and Criteria Change

After 30 days, the TRO reports that no donors have been found suitable for the research project among more than 200 referrals. The TRO reports that PMI is the major factor that caused the cases to be unsuitable and estimated that research recoveries could practically be completed in less than 6 hours from death. Concerned about the project timeline, the researcher agrees to increase the PMI to 6 hours with the hope of acquiring some tissue samples more quickly to begin experiments on schedule. The researcher indicates that her laboratory will be able to test RNA quality and determine if a 6-hour PMI will provide adequate quality of materials.

Donor screening resumes under the modified PMI criteria, and within the following 6 days a suitable donor is identified.

Research Donor Identification and NOK Consent

The first suitable donor based on the new criteria is a 38-year-old male motor vehicle accident victim who was pronounced brain dead in the emergency room of a local medical center. The hospital reported the donor's death to the State OPO, which approached the family for organ, tissue, and research tissue donation. During this period, the donor's heart and organs were maintained by means of a ventilator. At roughly 4 hours after being declared brain-dead, the OPO obtained consent from the deceased's NOK. The family consented to the donation of all organs and tissues for transplant and for research purposes with the exception of brain tissue for research, as they expressed concern that the recovery of brain tissue may impact their ability to have an open-casket funeral.

Organ Recovery

From the emergency room, the donor was transported to the surgical suite where the organ recovery team had assembled. The transplant surgeon and team completed the recovery of the donor's heart, lung, liver, and kidneys. All organs for transplant were recovered within less than 1 hour from the time of aortic cross-clamp (official time of donor death) and prepared for transit to waiting recipients and transplant teams in several other cities.

Tissue Recovery for Transplant

While the donor was undergoing organ recovery, an on-call team of three CTBS-certified tissue recovery specialists from the TRO were notified of the donor's availability and the impending tissue and research recovery. This mobile team set out to collect the necessary tissue and research recovery kits, supplies, and liquid nitrogen from their central office and laboratory, and then headed toward the medical center where the donor was located. It was estimated that it would take roughly 2 to 3 hours for the recovery team to arrive at the medical center.

By roughly 4 hours after the donor was declared dead, the TRO technicians arrived at the medical center with their supplies, liquid nitrogen Dewar flask, and dry ice and were beginning the recovery of long bones, dermatomed skin, saphenous vein, and corneas. This team included two individuals who had received specialized training in the recovery, preparation, and freezing of tissues for research.

The recovery of tissues for research began at roughly 4.5 hours after the donor's declared time of death. The team knew that, according to the project specifications, they had only 1.5 hours to recover all the requested research tissues to stay within an overall PMI of 6 hours as had been agreed upon with the researcher.

Research Biospecimen Recovery

After tissue recovery for transplant was completed, one of the specially trained recovery technicians prepared the donor and began excising the key organs according to the research project requirements. This technician focused on those organs that were most easily accessible within the donor's body cavity. This technician passed the recovered organs to the second specially trained recovery technician, who was working at the fine dissection and freezing in liquid nitrogen on a back table. The third technician supported research sample recovery by keeping written records of each sample type, sample tube identifiers, and freezing times. This technician also reviewed the donor's medical chart to ensure that he was free of chronic disease (exclusion criteria) to complete the requested items in the CRF supplied for the project.

The team worked for 1.5 hours, collecting and freezing research tissue samples. They chose to stop once the maximum time had elapsed. They collected nearly 100 frozen tissue samples from the following 12 anatomic sites:

1. Artery
2. Urinary bladder
3. Bone
4. Colon
5. Lymph node
6. Muscle
7. Pancreas
8. Skin
9. Spleen
10. Testis
11. Ureter
12. Vein (saphenous)

Consent had not been given by the family for donation of neurological tissues, so no attempt was made to recover tissue from the brain, pituitary, or spinal cord. Because the donor had previously undergone organ recovery for transplant, the following tissues were not available to the TRO team despite the fact they had been requested by the researcher:

- Heart (recovered for transplant)
- Lung (recovered for transplant)
- Liver (recovered for transplant)
- Kidney (recovered for transplant)
- Eye (recovered for transplant)
- Aorta (not available)
- Adrenal gland (not available)

Because overall timing did not permit additional complicated dissections the following tissues were not collected:

- Bone marrow
- Meniscus
- Cartilage
- Thymus
- Parathyroid
- Thyroid
- Nerve
- Prostate

The recovered research biospecimens were kept on dry ice after snap-freezing in liquid nitrogen and transported to an ultra-low -80 °C freezer at the TRO's central office and laboratory. The samples were then shipped on dry ice the following Monday to the researcher.

Upon RNA testing, the recovered materials were found to be adequate for the intended research purpose.

Summary of Lessons Learned from Case Study #1:

1. Increasing the acceptable PMI may permit more donors to qualify for recovery sooner and accelerate research biospecimen accrual.
2. The routine collection of numerous biospecimens from a broad assortment of tissues can be labor intensive and time consuming and may not always be feasible for every donor.
3. Many factors in addition to PMI may affect RNA quality.
4. Certain tissues recovered from donors may be set aside for transplantation and may not be available for research.

Case Study #2

Collection of Normal Postmortem Liver Tissues

A pharmacology researcher at an academic medical center seeks to test the toxicity effects of a number of different chemical compounds on human liver cells (hepatocytes). To accomplish this, the researcher requires a routine supply of normal fresh liver tissue to carry out tissue culture experiments. He collaborates with a departmental colleague pathologist, who, in collaboration with an oncologist, also oversees a rapid autopsy program for the recovery of widely metastatic cancers from individuals who have died from cancer.

The local IRB has approved the pharmacology research protocol in conjunction with the ongoing oncology protocol. The pharmacology researcher has specified minimum donor exclusion criteria—the liver must be free of grossly visible disease, including tumor metastases. Only minimal clinical data, including donor age, gender, and cause of death, are required.

With these criteria in place, the researcher begins receiving several normal fresh liver tissue samples (lobes of liver) each month from individuals who have died from cancer. Many of the liver specimens from the rapid autopsy cases are deemed unsuitable for the project, however, because the donor either had a history of cancer with tumors that had metastasized to liver or because metastatic tumors were found on gross examination of the liver during rapid autopsy. However, tumors in these livers were of value to the oncology research team and were procured.

Several months into the study, with adequate liver tissues obtained, the researcher observed a high degree of variability in his experimental data and found it difficult to reproduce results. Under the permissions granted for the project by the local IRB, the researcher investigated the medical histories of the postmortem donors who contributed fresh normal liver tissues to his experiments. The researcher found a recurring pattern—many individuals had been placed on multiple medications, including a variety of strong sedatives and painkillers, prior to their death. These medications may have contributed to additional variation in the experimental results.

To better control for this phenomenon and to improve the quality of his experimental results, the pharmacology researcher began working with the rapid autopsy program clinical research coordinator to prescreen donors based on their medication histories. This strategy resulted in fewer donors but improved experimental results.

To obtain additional samples, the researcher expanded his collaboration with the pathologist and obtained an amended IRB approval to collect additional fresh surplus liver tissue samples that were collected from normal tissue adjacent to resected liver tumors from living surgical tissue donors.

Summary of Lessons Learned From Case Study #2:

1. Iatrogenic effects can significantly impact research biospecimen quality and downstream research results.
2. Donor medical information used to screen eligible cases should be defined by the requirements of the specific research study for which they are intended.
3. To the extent possible, it is important to define inclusion and exclusion criteria that can rule out confounding variables that may impact research study end points.
4. The collection of certain postmortem research tissues can be supplemented through surgical research tissue collection.

APPENDIX E

Recommended Postmortem Research Recovery Collection Kit and Supplies

The following lists describe the typical contents for premade, single-use postmortem tissue recovery kits (including personal protective equipment and disposable supplies), shipping supplies, bulk disposables supplies, reagents, and reusable equipment.

DISPOSABLE SUPPLIES

(Recovery Kit Contents)

Quantity

Item

Disposables

4	Face shield, disposable
4	Surgical gown, disposable
36	Gloves, latex (12 pr. ea. S, M, L)
4	Sleeve protectors (set)
4	Shoe protectors (set)
4	Biohazard waste bags
6	Disposable surgical basin, plastic
10	12 in. x12 in. foam or plastic trays
10	Blue pads
2	Parafilm (1-ft. strip)
4	Specimen jars, 500 mL
12	Disposable scalpels (#22)

Data Collection & Shipping Docs

1	Blank CRF
1	Tissue sample accrual/tracking form
1	Preaddressed express courier shipping label
1	Preaddressed standard shipping label
3	Preaddressed shipping envelope
1	Pen(s), ball point
1	Xylene-resistant marker
1	Marking pen, Sharpie, extra-fine
1	Dry ice sticker

General Blood Collection Supplies

2	Syringes, 60cc
4	Needles, 16 gauge (long)
6	Alcohol pads

Quantity

Item

Supplies for Serology Blood

1	Blood collection tube shipping box
Var.	Blood tubes (as needed)
1	Company serological services request form
1	Express courier padded envelope
1	Express courier shipping label

Supplies for Research Blood

1	Blood collection tube shipping box
Var.	Blood tubes (as needed)
1	Blood collection form
1	Express courier padded envelope
1	Express courier shipping label

STOCK/BULK SUPPLIES

(as needed for specific research recovery protocols)

- 2.0-mL screw-top cryovials (external threads)
- Prelabeled standard-size histology cassettes
- Prelabeled super-size histology cassettes—mega cassettes (large)
- Additional scalpel blades
- Sterile conical tubes (50 mL)
- Sterile biospecimen jars
- Liquid-tight, screw-top shipping jars
- Large shipping boxes, insulated
- Small shipping boxes, insulated

STOCK REAGENTS

(as needed for specific research recovery protocols)

- Dry ice (pellets)
- Liquid nitrogen and CO₂
- 10% buffered formalin
- Wet ice
- Blue ice packs (chilled)
- Tissue transport media
- OCT
- Isopentane

REUSABLE SUPPLIES/EQUIPMENT

(Washable/Autoclavable)

- Spray bottle of alcohol (70% ethanol)
- 18 in. x 24 in. Teflon cutting/dissection board
- Bone saw
- Forceps (6 to 8 in.)
- Forceps (18 in.)
- Scissors
- Knife (brain knife)
- Sharps disposal container

APPENDIX F

Common Normal Research Tissues for Collection (Normal Tissue Panel)

The following list shows 57 normal tissue types that are commonly collected for cancer research. The complete panel of tissues may be collected from one or more postmortem donors. Given the amount of time that may be necessary to collect large panels from a donor, it is recommended to record the time elapsed between recovery of tissue from the donor and freezing of the tissue.

Alphabetical List—57 Tissue Types

1. Adipose
2. Adrenal gland
3. Anus
4. Aorta
5. Bile duct
6. Bone
7. Bone marrow
8. Brain (cerebellum and cerebral cortex)
9. Breast (F)—not cystic or fatty regions
10. Bronchi
11. Buccal mucosa
12. Cartilage
13. Cervix (F)
14. Colon
15. Esophagus—squamous, not GE junction
16. Eye
17. Fallopian tube (F)
18. Gall bladder
19. Heart
20. Kidney—cortex and medulla
21. Larynx
22. Liver
23. Lung, parenchyma
24. Lymph node
25. Muscle, skeletal
26. Nerve
27. Ovary (F)
28. Pancreas
29. Parathyroid
30. Penis (M)—glans and shaft
31. Pericardium
32. Peripheral nerve
33. Pharynx
34. Pituitary

35. Prostate (M)
36. Rectum
37. Salivary gland
38. Skin, abdominal
39. Small intestine
40. Spinal cord
41. Spinal nerve
42. Spleen
43. Stomach—cardia, fundus, and antrum
44. Tendon
45. Testis (M)
46. Thymus
47. Thyroid
48. Tongue
49. Trachea
50. Ureter
51. Urinary bladder
52. Uterus, endometrium (F)
53. Uterus, myometrium (F)
54. Vagina (F)
55. Vein (saphenous)
56. Vulva (F)
57. Whole blood

Example Prioritized Tissue List for Cancer Research—57 Tissue Types

The following list includes 57 normal tissue types that are commonly collected for cancer research. The list features (1) an example prioritization of tissues (first, second, third priority) that can guide recovery under circumstances when timing does not permit the collection of all tissues, (2) a description of the organ system from which the tissue is collected, and (3) a description of the dissection region of the donor that may serve to facilitate recovery work within multimember recovery teams.

Tissue Type	Example Collection Priority of Normal Tissue for Cancer Research			Organ System	Dissection Region
	1 st	2 nd	3 rd		
Whole Blood	1				
Trachea			1	Respiratory	Thoracic/Abdominal Block
Bronchi	1				
Lung, parenchyma			1		
Heart		1		Cardiovascular	
Aorta		1			
Pericardium		1			
Esophagus	1			Gastrointestinal	
Stomach	1				
Adipose		1			
Small intestine		1			
Colon	1				
Rectum	1				
Liver	1			Hepatobiliary	
Gall bladder			1		
Bile duct			1		
Pancreas	1			Endocrine	
Spleen		1		Hematopoietic	
Lymph node	1				
Kidney	1			Genito/Urinary	Abdominal Cavity
Adrenal gland		1		Endocrine	
Ovary (F)	1			Genito/Urinary	Pelvic Cavity
Fallopian tube (F)			1		
Uterus, endometrium (F)		1			
Uterus, myometrium (F)		1			
Cervix (F)		1			
Vagina (F)			1		

Best Practices for Postmortem Recovery of Normal Human Tissue for Research

Vulva (F)			1		
Urinary bladder		1			
Ureter			1		
Prostate (M)	1				
Brain (cerebellum and cerebral cortex)	1			Central/Peripheral Nervous	Head/Neck
Pituitary		1		Endocrine	
Eye			1	Central/Peripheral Nervous	
Nerve			1		
Spinal cord	1				
Spinal nerve		1			
Larynx			1	Respiratory	
Pharynx			1		
Salivary gland		1		Endocrine	
Thyroid	1				
Parathyroid			1		
Thymus			1	Hematopoietic	
Muscle, skeletal	1			Musculoskeletal	Limb (Leg)
Tendon			1		
Cartilage			1		
Bone		1			
Vein (saphenous)			1	Cardiovascular	
Peripheral nerve		1		Peripheral Nervous	
Bone marrow	1			Hematopoietic	
Buccal mucosa		1		Respiratory	External
Tongue			1	Musculoskeletal	
Breast (F)	1			Integument	
Skin	1				
Penis (M)			1	Genito/Urinary	
Testis (M)	1				
Anus			1	Gastrointestinal	

Total Tissue

Types by

Collection Priority 20 17 20

Normal Tissue Panels (Comparator Tissues) for Commonly Researched Diseases

The following lists of normal tissues include those tissues commonly requested by researchers for studies in the indicated therapeutic areas.

Tissues listed by therapeutic area and shown in alphabetical order.

Neurologic Disease Research

1. Accumbens - L & R
2. Amygdala - L & R
3. Caudate nucleus - L & R
4. Cerebellum - L & R
5. Cingulum bundle - L & R
6. Dorsolateral frontal cortex (Brodmann area 10) - L & R
7. Dorsolateral frontal cortex (Brodmann area 9) - L & R
8. Entorhinal cortex (Brodmann area 28) - L & R
9. Globus pallidus externa - L & R
10. Globus pallidus interna - L & R
11. Hippocampus - L & R
12. Hypothalamus
13. Inferior temporal gyrus (Brodmann area 20) - L & R
14. Medulla
15. Middle temporal gyrus (Brodmann area 21) - L & R
16. Occipital cortex - L & R
17. Pituitary gland
18. Precentral gyrus (Brodmann area 4) - L & R
19. Precentral gyrus (Brodmann area 6) - L & R
20. Putamen - L & R
21. Raphe nucleus
22. Spinal cord
23. Substantia nigra - L & R
24. Subthalamic nucleus - L & R
25. Temporal tip (Brodmann area 38) - L & R
26. Thalamus - L & R
27. Vermis

Cardiovascular Disease Research

1. Aorta - abdominal
2. Aorta - thoracic
3. Atria - L & R
4. Carotid artery
5. Coronary artery - L & R
6. Femoral artery
7. Mitral valve
8. Pericardium
9. Pulmonary artery - L & R
10. Renal artery
11. Saphenous vein
12. Ventricle - L & R

Respiratory Disease Research

1. Bronchus - L & R
2. Diaphragm
3. Larynx
4. Lung, left lower lobe
5. Lung, left upper lobe
6. Lung, right lower lobe
7. Lung, right middle lobe
8. Lung, right upper lobe
9. Nasal mucosa
10. Trachea

Metabolic Disease Research

1. Adipose - abdominal
2. Adipose - omental
3. Adipose - subcutaneous
4. Adrenal gland
5. Liver
6. Pancreas
7. Stomach
8. Thyroid

Inflammatory Disease Research

Rheumatoid and Osteoarthritis:

1. Bone, cortical
2. Cartilage
3. Meniscus
4. Synovium
5. Tendon

Crohn's Disease and Ulcerative Colitis:

1. Colon
2. Duodenum
3. Ilium
4. Jejunum

Lupus:

1. Kidney (cortex and medulla)
2. Skin (full thickness sections)

APPENDIX G

Biospecimen Collection and Preparation Guidelines

The following guidelines describe methods for the standardized collection and preparation of frozen and fixed tissue biospecimens and blood samples.

1. Basic Postmortem Recovery Information

- Agonal state information (e.g., fever, hypotension, hypoxia, oxygen supplementation, cyanosis, O₂ saturation, medications in the last days to weeks of life), if available, can be recorded.⁴⁹
- The PMI (the number of hours from death until autopsy or until the specimen is fixed/frozen, depending on which measurement is standard in the specific laboratory) should be recorded.

2. Acquisition and Processing of Tissue Biospecimens

- Multiple biospecimens from each tissue type (based on size of anatomical structure) should be collected. Dissection should be carried out as soon as possible after the specimen is removed from the donor.
- Tissue samples for freezing and formalin fixation can be collected and prepared as follows:
 - Dissect fresh tissue to 1.0 cm x 1.0 cm x 1.5 cm in size.
 - Remove a 1.0 cm x 1.0 cm x 0.5 cm “top” slice from prepared fresh tissue.
 - Place the 1.0 cm x 1.0 cm x 0.5 cm “top” slice (cut-face down) in an appropriately labeled histology cassette and place into 10% phosphate-buffered neutral formalin (formalin fixed sample)
 - Place the resulting 1.0 cm x 1.0 cm x 1.0 cm tissue cube (cut-face down) into an appropriately-labeled biospecimen container and immediately snap-freeze in liquid nitrogen (frozen sample)
 - Repeat steps above for multiple replicate samples.
- Frozen biospecimen containers should be stored temporarily in liquid nitrogen or on dry ice until shipped.
- Collection of samples in OCT or other types of media, fixative, or biospecimen containers may be appropriate as needed for specific research projects.

- Appropriate and complete documentation surrounding biospecimen collection, processing, and storage is essential and will influence the quality of research data to be obtained.
- Bioanalysis for quality control (e.g., standard assays for RNA integrity) is recommended using as little of the specimen as possible.

3. **Acquisition and Processing of Blood Biospecimens**

- For most purposes, blood may be drawn using a vacutainer system into a series of tubes of typical volume (5 to 10 mL).
- A large volume of blood should be drawn directly from the vena cava (via open thoracic cavity) using a 60-cc syringe and wide-gauge needle. The needle should then be removed and the appropriate volume of blood expelled from the syringe into each required tube type.
- The choice of anticoagulant is important. Vacutainer tubes are manufactured with anticoagulants added. Options when using plasma include ethylenediaminetetraacetic acid or heparin; no anticoagulant is added to prepare serum.
- Standardized and uniform techniques for sample processing are recommended.
- Rapid processing of samples is optimal. Centrifugation may be carried out within 30 minutes to 24 hours of blood draw followed by aliquoting of samples into the storage tubes then freezing and transferring to -80 °C storage.
- Appropriate and complete documentation surrounding biospecimen collection, processing, and storage is essential and will influence the quality of research data to be obtained.

Common Tube Types for Blood Biospecimens

<u>Tube Types</u>	<u>Typical Volume</u>	<u>Standard Applications</u>
“Red-Top” Tube	10 mL	Serum preparation
“Lavender/Purple-Top” Tube	10 mL	Plasma prep/Cell pellet
PAXGene RNA Tube	2.5 mL	RNA extraction
PAXGene DNA Tube	8.5 mL	DNA extraction
P-100	8.5 mL	Proteomics

APPENDIX H

Variables That May Affect the Quality of Postmortem Research Tissues

The following list contains the most common variables that can impact postmortem tissue quality for research.

- Donor's age at death
- Mode of death
- Nutritional state
- Agonal state and duration
- Fever
- Use of ventilator, mechanical support, or organ perfusion support
- Oxygen supplementation
- Hypoxia
- Hypotension
- Medical history (comorbid factors)
- Medications
- Blood pH
- Hardy Scale
- Ischemic start time
- Emergency procedures
- Body storage conditions
- PMI

APPENDIX I

Potential Data for Postmortem Research Biospecimen Recovery

The following list describes potential data elements that may be collected for research studies utilizing postmortem biospecimens. As an additional reference, UNOS publishes a complete list of organ- and donor type-specific data collection forms for organ transplantation.⁵⁰

Donor Demographic Information

- Date of birth (age)
- Gender
- Race/ethnicity
- Height
- Weight

Behavioral and Social Information

- Social history (lifestyle and travel)
- Smoking history
- Alcohol use
- Recreational drug use
- Special diet
- Environmental exposures

Medical Information

- Previous medical conditions (date of diagnosis and treatment history, if known)
- Current/recent medical conditions (date of diagnosis and treatment history, if known)
- Laboratory and medical tests during current or previous hospitalizations
- Medications (insulin, etc.)
- Anesthesia information
- Allergies
- Psychiatric/neurodegenerative conditions
- Menstrual and obstetric history
- Hormone replacement therapy
- Time on ventilator
- Familial disease history, if known

Other Medical Records (if available)

- Pathology report information
- Clinical trial CRFs (noting chemotherapy, radiation, or other)
- Hospice record information
- Emergency room/admitting record information

Infectious Disease/Serology Information

- HIV, HTLV, HCV, HBV, RPR, ABO
- Blood cultures

Postmortem Information

- Date and time of death
- Cause of death (death report/certificate data)
- Body storage conditions
- Funeral wishes/arrangement information

Biospecimen Recovery Information

- Date and time of tissue recovery
- Autopsy (Y/N)
- Organ donor status (Y/N)—organs donated
- Tissue donor status (Y/N)—tissues donated
- Date and time of aortic cross-clamp
- Date and time of initial sample preservation
- Date and time of final sample preservation
- PMI
- Donor identification code
- Biospecimen identification codes (linked to donor ID)
- Courier shipment tracking numbers

APPENDIX J

Recovery Team Staffing Descriptions

The following describes typical staff and responsibilities affiliated with academic research, OPO, and TRO research tissue recovery programs.

Academic Research Programs (Rapid Autopsy Programs)

- **Consent Nurse Coordinator.** Most importantly, these individuals are often involved in essential duties that have been traditionally performed by the PI, such as conducting the informed consent process and ensuring compliance with the protocol.
- **Diener.** An individual at the morgue who is responsible for handling, moving, and cleaning the corpse (at some institutions, dieners perform the entire dissection at autopsy). The term diener derives from the German word *Leichendiener*, which translates as “corpse servant.”
- **Pathologist.** A medical expert who is concerned with the diagnosis of disease based on the gross, microscopic, chemical, immunologic, and molecular examination of organs, tissues, and whole bodies (autopsy).
- **Pathologist’s Assistant.** An individual trained in the gross examination of surgical or postmortem specimens to gather diagnostically critical information, including the stage and margin status of surgically removed tumors.
- **Postdoctoral Student/Fellow.** An individual who has completed doctoral studies and who seeks to deepen expertise as a specialist and may be funded through an appointment with a salary, stipend, or sponsorship award.
- **Research Assistant/Associate.** An individual employed, often on a temporary contract, by a university or a research institute for the purpose of assisting or conducting in academic research.
- **Histotechnologist.** An individual experienced in the handling and processing of tissues for use in diagnostic examination and research.
- **Clinical Data Coordinator.** An individual trained for, and with access to, the collection of clinical data from the donor’s electronic and/or paper-based medical record.

Organ Procurement Organizations

- **Medical Director.** The OPO Medical Director is responsible for the clinical oversight and medical quality assurance of the OPO recovery program.

- **Clinical Recovery Coordinator.** This individual is responsible for the duties related to the evaluation, allocation, and surgical recovery of organs and tissues for transplantation, medical research, and medical education. Clinical responsibilities include donor evaluation and clinical management, organ and tissue evaluation and allocation, and the surgical recovery and preservation of donated organs and tissues

Tissue Recovery Organizations

- **Tissue Recovery Specialist.** An individual responsible for the recovery, preservation, and packaging of human tissues; the reconstruction of deceased donors following tissue recovery; and donor chart review and the completion of paperwork associated with tissue recovery. The tissue recovery specialist may also be responsible for assisting in receiving, screening, and processing referral calls from local area hospitals for donation. This professional category includes those individuals with a professional certification; e.g., a CTBS conferred by the AATB.
- **Donation Specialist/Consent Coordinator.** The donation specialist is responsible for the duties related to the donation and recovery of tissue for transplantation, research, and education. Specific responsibilities may include answering referral telephone calls from area hospitals, evaluating the medical suitability of potential organ and tissue donors, offering the option of tissue donation to the NOK, and coordinating the surgical recovery of any donated tissue for transplantation and/or research. Additional responsibilities include contacting the ME to obtain permission for the donation of tissue for transplantation or research and/or contacting the local tissue and eye banks to provide referral/donation information and performing QA on tissue donation charts and paperwork.

APPENDIX K

General Health and Safety Considerations

The following describes general health and safety considerations that should be implemented for postmortem research tissue recovery programs.

1. Recovery organizations should have safety plans as described in the *NCI Best Practices for Biospecimen Research*.
2. Recovery personnel should have:
 - a. Immunization for hepatitis B (recommended) and tetanus
 - b. Training in safety procedures related to handling of human tissue
 - c. Training in Universal Precautions—all specimens must be handled as if infectious
 - d. Training in the safe use of tissue processing reagents (e.g., formalin, dry ice, isopentane, liquid nitrogen)
 - e. Training in post-incident response
 - f. Training as required by local, state, and Federal authorities (e.g., Occupational Safety and Health Administration)
 - g. Training in International Air Transport Association compliance
3. Biospecimen Safety Precautions
 - a. It is recommended that a disclaimer accompany all biospecimen disbursements, even if tested negative for HIV and hepatitis B and C. The disclaimer should indicate that recipients understand that absence of infectivity of biospecimens cannot be guaranteed, that the laboratory warrants that personnel have been trained in procedures related to handling of human tissue, and that universal precautions will be observed.
 - b. HIV and hepatitis B and C
 - i. Testing of blood for hepatitis and HIV may be performed, if desired. However, false positives and false negatives may occur; therefore, a negative test for hepatitis or HIV does not guarantee the absence of infectivity.
 - ii. Cases with a history of hepatitis B or C or HIV infection may be excluded.
 - iii. It is recommended that frozen tissue, blood, and DNA not be distributed from cases positive for hepatitis or HIV unless a study specifically requires this type of

tissue. These tissues may be kept and labeled as either hepatitis or HIV positive for such needs.

APPENDIX L

Example Simple Letter Agreement for the Transfer of Materials

In response to the RECIPIENT's request for the MATERIAL [insert description] the PROVIDER asks that the RECIPIENT and the RECIPIENT SCIENTIST agree to the following before the RECIPIENT receives the MATERIAL:

The above MATERIAL is the property of the PROVIDER and is made available as a service to the research community.

THIS MATERIAL IS NOT FOR USE IN HUMAN SUBJECTS.

The MATERIAL will be used for teaching or not-for-profit research purposes only.

The MATERIAL will not be further distributed to others without the PROVIDER's written consent. The RECIPIENT shall refer any request for the MATERIAL to the PROVIDER. To the extent supplies are available, the PROVIDER or the PROVIDER SCIENTIST agree to make the MATERIAL available, under a separate Simple Letter Agreement to other scientists for teaching or not-for-profit research purposes only.

The RECIPIENT agrees to acknowledge the source of the MATERIAL in any publications reporting use of it.

Any MATERIAL delivered pursuant to this Agreement is understood to be experimental in nature and may have hazardous properties. THE PROVIDER MAKES NO REPRESENTATIONS AND EXTENDS NO WARRANTIES OF ANY KIND, EITHER EXPRESSED OR IMPLIED. THERE ARE NO EXPRESS OR IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR THAT THE USE OF THE MATERIAL WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER PROPRIETARY RIGHTS. Unless prohibited by law, Recipient assumes all liability for claims for damages against it by third parties which may arise from the use, storage or disposal of the Material except that, to the extent permitted by law, the Provider shall be liable to the Recipient when the damage is caused by the gross negligence or willful misconduct of the Provider.

The RECIPIENT agrees to use the MATERIAL in compliance with all applicable statutes and regulations.

The MATERIAL is provided at no cost, or with an optional transmittal fee solely to reimburse the PROVIDER for its preparation and distribution costs. If a fee is requested, the amount will be indicated here: [insert fee].

The PROVIDER, RECIPIENT and RECIPIENT SCIENTIST must sign both copies of this letter and return one signed copy to the PROVIDER. The PROVIDER will then send the MATERIAL.

PROVIDER INFORMATION

Provider Scientist:
Provider Organization:
Address:

RECIPIENT INFORMATION and AUTHORIZED SIGNATURE

Recipient Scientist:
Recipient Organization:
Address:
Name of Authorized Official:
Title of Authorized Official:
Signature of Authorized Official:
Date:

Certification of Recipient Scientist: I have read and understood the conditions outlined in this Agreement and I agree to abide by them in the receipt and use of the MATERIAL.

Recipient Scientist:
Date:

Example Materials Transfer Agreement

PUBLIC HEALTH SERVICE

MATERIAL TRANSFER AGREEMENT

This Public Health Service ("PHS") model Material Transfer Agreement ("MTA") has been adopted for use for transfer of materials collected pursuant to contracts awarded by the National Institute of Child Health and Development ("NICHD").

Additional terms added by the NICHD Brain and Tissue Bank to the PHS MTA, other than names, addresses and answers to specific questions, are indicated by a line in the margin.

Provider: University of Maryland, Baltimore through its NICHD Brain and Tissue Bank for Developmental Disorders ("**Brain and Tissue Bank**"). Supported by NICHD contract # NO1-HD-4-3368 and N01-HD-4-3383.

Recipient: Enter Name of Institution

1. **Provider** agrees to transfer to Recipient's Investigator ("**Investigator**") named below the following **Research Material**:

Research Material: Human tissue

Name of Investigator:

2. **THIS RESEARCH MATERIAL MAY NOT BE USED IN HUMAN SUBJECTS.** The **Research Material** will only be used for research purposes by **Investigator** in his/her laboratory, for the research project described below, under suitable containment conditions. This **Research Material** will not be used for commercial purposes such as screening, production or sale, for which a commercialization license may be required. **Investigator** agrees to comply with all Federal rules and regulations applicable to the **Research Project** and the handling of the **Research Material**.

2(a). Are the Research Materials of human origin?

☒ Yes

☐ No

2(b). If Yes in 2(a), were **Research Materials** collected according to 45 CFR Part 46, "Protection of Human Subjects"?

X Yes (Please provide Assurance Number: 1298035)

 No

3. This **Research Material** will be used by **Investigator** solely in connection with the following research project ("**Research Project**") described with specificity as follows (use an attachment page if necessary):

4. In all oral presentations or written publications concerning the **Research Project**, **Investigator** will acknowledge **Provider's** contribution of this **Research Material** unless requested otherwise. To the extent permitted by law, **Investigator** agrees to treat in confidence, for a period of three (3) years from the date of its disclosure, any of **Provider's** written information about this **Research Material** that is stamped "**CONFIDENTIAL**," except for information that was previously known to **Investigator** or that is or becomes publicly available or which is disclosed to **Investigator** without a confidentiality obligation. Any oral disclosures from **Provider** to **Investigator** shall be identified as being **CONFIDENTIAL** by notice delivered to **Investigator** within ten (10) days after the date of the oral disclosure. **Investigator** may publish or otherwise publicly disclose the results of the **Research Project**, but if **Provider** has given **CONFIDENTIAL** information to **Investigator** such public disclosure may be made only after **Provider** has had thirty (30) days to review the proposed disclosure to determine if it includes any **CONFIDENTIAL** information, except when a shortened time period under court order or the Freedom of Information Act pertains.

5. This **Research Material** represents a significant investment on the part of **Provider** and is considered proprietary to **Provider**. **Investigator** therefore agrees to retain control over this **Research Material** and further agrees not to transfer the **Research Material** to other people not under her or his direct supervision without advance written approval of **Provider**. **Provider** reserves the right to distribute the **Research Material** to others and to use it for its own purposes. When the **Research Project** is completed or three (3) years have elapsed, whichever occurs first, the **Research Material** will be disposed of as directed by **Provider**.

6. This **Research Material** is provided as a service to the research community. IT IS BEING SUPPLIED TO RECIPIENT AND INVESTIGATOR WITH NO WARRANTIES, EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. **Provider** makes no representations that the use of the **Research Material** will not infringe any patent or proprietary rights of third parties.

7. When **Provider** is the PHS: Not applicable.

8. When **Recipient** is the PHS: The **PHS** shall retain title to any patent or other intellectual property rights in inventions made by its employees in the course of the **Research Project**. The **PHS** is not authorized to promise rights in advance for inventions developed under this Agreement. **Provider** acquires no intellectual property rights under this MTA, but may apply for

license rights to any patentable invention that might result from this **Research Project**. It is the intention of **PHS** that **Provider** not be liable to **PHS** for any claims or damages arising from **PHS's** use of the **Research Material**; however, no indemnification is provided or intended.

9. The undersigned **Provider, Recipient, and Investigator** expressly certify and affirm that the contents of any statements made herein are truthful and accurate.

10. When the recipient is the PHS: this MTA shall be construed in accordance with Federal law as applied by the Federal courts in the District of Columbia.

11. Any additional terms:

In accordance with the requirements of NIH Contract No. N01-HD-4-3368 to the University of Maryland, **Investigator** will:

- (a) utilize the tissue for research for the general welfare. It is the intent of the **Investigator** to publish meaningful results from this research in the public domain such as in a scientific journal, to present the results at a scientific meeting, or to make a presentation open to the public.
- (b) acknowledge the **NICHD Brain and Tissue Bank for Developmental Disorders and NICHD Contract No. N01-HD-4-3368 and N01-HD-4-3383** in any and all publications based on data derived from research involving the **Research Material** by inclusion of the following in the acknowledgement section of publications: "Human tissue was obtained from the NICHD Brain and Tissue Bank for Developmental Disorders at the University of Maryland, Baltimore, MD. The role of the NICHD Brain and Tissue Bank is to distribute tissue, and therefore, cannot endorse the studies performed or the interpretation of results."
- (c) send the **Provider** a copy of any scientific publication resulting from research involving the **Research Material**. These publications will be used by the **Provider** for technical progress reports to the NIH.
- (d) compensate the **Brain and Tissue Bank** for handling and processing the **Research Material** at the following rates: Non-profit institutions - \$75 per specimen from infants/children/adults plus shipping costs. For-profit organizations - \$250 per specimen from infants/children/adults plus shipping. Special requests may alter the handling fees on a case-by-case basis.
- (e) **Recipient and Investigator** recognize the potential hazard of utilizing human tissues and understand that the appropriate precautions to minimize any health risk become fully their responsibility. In no event shall the **Brain and Tissue Bank** or the **Director** or their respective trustee's, officers, agents, employees, students, heirs, representatives or assignees be liable for any use, loss, claim, damage or liability of whatsoever kind or nature which may arise from or in connection with this Agreement or the use, shipping, receipt, handling or storage of **Research Material** by **Recipient and Investigator**. **Recipient and Investigator** understand that the **Brain and Tissue Bank** will take all reasonable precautions to ensure proper packaging of **Research Material** for shipping purposes. The **Brain and Tissue Bank**, however, is not liable for any damages to or incurred by the shipping of **Research Material** either while en route or once received by **Investigator**.
- (f) In place of a signature from an "Authorized Official," the **Investigator** may provide a copy of a letter/notification that its institutional review board has approved the **Research Project**. If

the Recipient is a for-profit organization, the signature of the Authorized Official will serve this purpose.

(g) Payment for tissue handling fees is expected by credit card or check in a timely manner.

Recipient Organization: _____

Date: _____
Investigator's Signature Title

Date: _____
Authorized Official's Signature for Recipient's Organization Title

Investigator's Mailing Address: YOU MUST INCLUDE YOUR MAILING ADDRESS BELOW:

Provider Organization: University of Maryland Baltimore through its NICHD Brain and Tissue Bank for Developmental Disorders

Date: _____
Signature of Director

Date: _____
Authorized Signature University of Maryland, Baltimore and Title

Provider's Mailing Address: NICHD Brain and Tissue Bank for Developmental Disorders
University of Maryland, Baltimore
Pediatric Research, 10-035 BRB
655 W. Baltimore Street
Baltimore, MD 21201-1559
410-706-1755 phone
410-706-0020 fax
btbumab@umaryland.edu
www.btbank.org

Any false or misleading statements made, presented, or submitted to the **Government**, including any relevant omissions, under this **Agreement** and during the course of negotiation of this **Agreement** are subject to all applicable civil and criminal statutes including Federal statutes 31 U.S.C. §§ 3801-3812 (civil liability) and 18 U.S.C. § 1001 (criminal liability including fine(s) and/or imprisonment).

APPENDIX M

Respectful Language Related to Tissue Donation

(Source: AOPO Donor Family Service Council)

As with many aspects of organ, eye, and tissue donation, respectful terminology is continually updated and changed. This is part of an evolving effort to convey facts using words and phrases that are not offensive to donor families.

~~cadaveric~~ / deceased

The families of organ and tissue donors have asked donor programs and news media to refrain from using the term “cadaveric donor.” The preferred term is “deceased donor.”

~~harvest or retrieval~~ / recover or recovery

Out of respect for the heroes who donate life, the term “recovery” should be used instead of “harvest” when referring to the surgical recovery of lifesaving and life-enhancing gifts. “Harvest” has negative connotations for patients and families.

~~life support~~ / ventilator, mechanical support, or organ-perfusion support

“Ventilator” is the accurate term to use when reporting on organ donation; a deceased donor remains on a ventilator to maintain organ function and therefore enable the sharing of life with others. It is incorrect to state that the deceased donor is on life support, as it gives the false impression that an individual is “kept alive” so that organs can be donated. This, of course, is never the case. Organs and tissue are only recovered from individuals whose death has been legally declared and consent has been given either through a donor document or at the request of the family.

~~non-heart-beating donation~~ / donation after cardiac death

Everyone has the opportunity to be a donor. After cardiac death, tissues may be donated for transplantation, therapy, and research. In some instances, a person may donate organs after cardiac death has occurred. This can occur if a patient has suffered devastating and unrecoverable brain damage that necessitates ventilator dependence, the family has decided to withdraw support, and death from cardiac and respiratory arrest will occur within one hour following the withdrawal of support. In this situation, organ recovery would occur only after support is withdrawn and after cardiac death is pronounced.

APPENDIX N

Sample Letter to Donor Families

DATE

Name

Address

Dear :

On behalf of everyone at the [insert name here], I would like to extend my most sincere condolences on the recent loss of your loved one. Dealing with death is never easy, but your ability to think of others in your time of sorrow is an undeniable testament to your compassion and love. The gift you unselfishly gave to others when you decided to donate your loved one's tissues for medical research was truly heroic.

The cells from various human organs and tissues are used in almost all medical research programs. These cells can test human reactions to diseases as well as test the drugs needed to cure them. Medical researchers are seeking cures for numerous diseases, from diabetes to heart disease to cancer—and the courageous decisions of donors and their families that ensure that there will be enough tissue to possibly cure these diseases in our lifetime.

Enclosed you will find several important documents. Be sure to read the letter from our finance department as well as the brochure from the recovery agency that facilitated the donation. You and your family will be a part of that agency's donor family aftercare program, which will provide resources and comfort as you go through this period. We have also enclosed the Donor Family Bill of Rights and a list of national bereavement resources that may be of some help.

Your generosity during this difficult time of loss allows us to provide the top medical research facilities in the country with tissue to continue their important and life-saving work. I hope that this can bring you comfort now and in the days ahead.

The thoughts of all of us are with you now and in the future.

Sincerely,

[Name]

APPENDIX O

Example Donor Family Relations Materials

(Source: National Donor Family Council 2002)

Donor Family Bill of Rights

Families have the right:

1. To a full and careful explanation about what has happened to their loved one, his or her current status, and his or her prognosis.
2. To be full partners with the health care team in the decision-making process about the care and support given to their loved one and to themselves.
3. To a full and careful explanation about how the (impending) death of their loved one was or will be determined with appropriate reference to the concepts of cardiac and/or brain death.
4. To be given opportunities to be alone with their loved one during his or her care and after his or her death occurs. This should include offering the family an opportunity to see, touch, hold or participate in the care of their loved one, as appropriate.
5. To be cared for in a manner that is sensitive to the family's needs and capacities by specially-trained individuals.
6. To be informed if their loved one had previously indicated an intent to donate organs and/or tissues and their family's responsibility to honor that decision.
7. To be given the opportunity to make organ and tissue donation decisions on behalf of their loved one, where appropriate and in accordance with applicable laws. This opportunity should be included in the normal continuum of care by the health care provider after death has been determined and the family has had sufficient time to acknowledge that death has occurred.
8. To receive information in a manner that is suited to the family's needs and capacities about the need for organ and tissue donation, the conditions and processes of organ and tissue donation and the implications of organ and tissue donation for later events, such as funeral arrangements, viewing of the body and related practices.
9. To be provided with time, privacy, freedom from coercion, confidentiality and (if desired) the services of an appropriate support person (e.g., clergyperson) and other resources (e.g., a second medical opinion, advice from significant others or the services of an interpreter for those who speak another language) which are essential to optimal care for the family.

10. To have opportunities to spend time alone with their loved one before and/or after the process of removing donated organs and/or tissues, and to say their 'goodbyes' in a manner that is appropriate to the present and future needs of the family, and consistent with their cultural and religious identity (e.g., asking the family if they want handprints, footprints, a lock of hair, etc.).
11. To be assured that their loved one will be treated with respect throughout the process of removing donated organs and/or tissues.
12. To receive basic written information from Organ Procurement Organizations (OPOs) and Tissue Recovery Organizations (TROs) either at the time of consent or in the days immediately following that decision. At a minimum, this written material should include a copy of the signed consent form(s), information on how the organs and tissues may be used, and instructions on how to follow up with the OPO or TRO in case concerns arise.
13. To receive timely information that is suited to the family's needs and capacities about which organs and/or tissues were or were not removed, and why.
14. To receive timely information regarding how any donated organs and/or tissues were used, upon request and whenever possible. If desired, families should be given an opportunity to exchange communications with individual recipients and/or recipient family members. Upon request, donor families should also be given accurate updates on the condition of the recipients.
15. To be assured that the donor family will not be burdened with any expenses arising from organ and/or tissue donation, and to be given assistance in resolving any charges that might be erroneously addressed to the family.
16. To receive ongoing bereavement follow-up support for a reasonable period of time. Such support might take the form of: the name, address and telephone number of a knowledgeable and sensitive person with whom they can discuss the entire experience; an opportunity to evaluate their experience through a quality assurance survey; free copies of literature about organ and tissue donation; free copies of literature about bereavement, grief and mourning; opportunities for contact with another donor family; opportunities to take part in a donor or bereavement support group and/or the services of a skilled and sensitive support person.

This document was prepared by Charles A. Corr, PhD, Lucy G. Nile, MA, and the members of the 1994 Executive Committee of the National Donor Family Council (NDFC) of the National Kidney Foundation.

Revised by the 2002 Executive Committee of the NDFC.

The Bill of Rights for Donor Families has been officially endorsed by the following organizations:

- American Association of Critical-Care Nurses
- Association of Organ Procurement Organizations
- Division of Transplantation, Health Resources & Services Administration, U.S. Department of Health & Human Services
- National Donor Family Council
- National Kidney Foundation
- North American Transplant Coordinators Organization

APPENDIX P

Sample Finance Letter to Donor Families

DATE

Name

Address

Dear :

The [insert name here] wishes to assure you that there is no cost to you, your family, or to your insurance carrier for the services involved in recovering or donating your loved one's organs or tissues for research.

Our finance office maintains regular contact with the finance department of the recovering agency to ensure that you and your insurance company are protected from receiving bills related to this donation.

Occasionally, a billing error is made, and a donor family receives inappropriate hospital, physician, or funeral home bills. If you receive any bills that you believe are related to the research donation of your loved one's organs or tissues, please contact either the recovering agency or our office as soon as possible. We will work closely to find the quickest solution possible.

It is our goal to provide needed tissues to the many researchers who strive diligently to find cures for devastating medical traumas and diseases. However, we are also committed to providing all donor families with much-deserved care and respect during this difficult time. Please do not hesitate to contact us with any financial issues.

Sincerely,

[name]

APPENDIX Q

Bereavement Resources

General Grief:

- www.griefcareprovider.com
- www.goodgrief.org
- www.healingthespirit.org
- www.hospicenet.org
- www.griefshare.org

Widowhood:

- www.widownet.org
- www.webhealing.com

Death of children:

- www.compassionatefriends.org
- www.bereavedparentsusa.org
- www.alivealone.org
- www.dougy.org

Death of infants and toddlers:

- www.firstcandle.org
- www.healingheart.net
- www.sidsandkids.org
- www.unitegriefsupport.org

Sibling loss:

- www.adultsiblinggrief.com
- www.tcfsiblingsupport.org
- www.cancer.net, search word “grief”

SUGGESTED READING

Grief (General):

- Kenneth J. Doka, *Living with Grief after Sudden Loss*
- Bill Dunn, *Through a Season of Grief*
- Stephanie Ericsson, *Companion through the Darkness*
- Linda Feinberg, *I'm Grieving as Fast as I Can*
- Helen Fitzgerald, *The Mourning Handbook*
- Earl A. Grollman, *Living When a Loved One has Died*
- Ashley D. Prend, *Transcending Loss*
- Therese A. Rando, *How to Go On Living When Someone You Love Dies*
- Pat Schweibert, *Tear Soup*
- John E. Welshons, *Awakening from Grief: Finding the Way Back to Joy*

Widowhood:

- Gustavo Acosta, *And Life Goes On... A Path through Widowhood*
- Joan Didion, *The Year of Magical Thinking*
- Marta Felber, *Finding Your Way after Your Spouse Dies*
- Pat Novak, *ABCs of Widowhood*

Loss of a Child:

- Jeanne Webster Davis, *The Death of an Adult Child*
- Ronald Knapp, *Beyond Endurance: When a Child Dies*
- Elizabeth Mehren, *After the Darkest Hour the Sun Will Shine Again: A Parent's Guide*
- Catherine Sanders, *How to Survive the Loss of a Child*

Helping Children and Teens:

- Helen Fitzgerald, *The Grieving Child: A Parent's Guide*
- Earl A. Grollman, *Bereaved Children and Teens*
- Earl A. Grollman, *Talking about Death: A Dialogue between Parent and Child*
- Alan D. Wolfelt, *Healing a Teen's Grieving Heart*

Suicide:

- Cain, *Survivors of Suicide*
- Eileen Kuehn, *After Suicide: Living with the Quest*
- Christopher Lukas, *Silent Grief: Living in the Wake of Suicide*
- Michael F. Myers, *Touched by Suicide: Hope and Healing After Loss*
- E. Betsy Ross, *Life After Suicide: A Ray of Hope for Those Left Behind*

Grief (Other):

- Tom Crider, *Give Sorrow Words: A Father's Passage Through Grief*
- Katherine F. Donnelly, *Surviving the Loss of a Parent*
- Margaret Gerner, *For Bereaved Grandparents*
- Tom Golden, *Swallowed by a Snake*
- Sherokee IIsed, *Coping with Holidays and Celebrations*

Writing Through Grief:

- John Fox, *Finding What You Didn't Lose: Expressing Your Truth and Creativity Through Poem Making*
- Katharine Peterson, *Write from Your Heart: A Healing Grief Journal*
- Susan Zimmerman, *Writing to Heal the Soul: Transforming Grief and Loss Through Writing*

APPENDIX R

Religious and Cultural Views on Organ Donation and Transplantation

(Adapted from OrganDonor.gov and Wisconsin Donor Network, *Organ and Tissue Donation: A Reference Guide for Clergy*, 1995)

AME & AME Zion (African Methodist Episcopal)

Organ and tissue donation is viewed as an act of neighborly love and charity by these denominations, which encourage all members to support donation as a way of helping others.

American Indian

Generally, American Indians do not desire organ donation or autopsy as they hold beliefs about the body having to remain intact to enter the spirit world.⁵¹ However, most tribes have ways to honor those beliefs when the body is not intact. Changes in tribal attitude toward organ donation are occurring due to the large numbers of American Indians and Alaskan Natives on renal dialysis due to diabetes-related end-stage renal disease.

Amish

The Amish consent to donation if they know it is for the health and welfare of the transplant recipient. They believe that since God created the human body, it is God who heals. However, they are not forbidden from using modern medical services, including surgery, hospitalization, dental work, anesthesia, blood transfusions, or immunization.

Assembly of God

The church has no official policy regarding donation. The decision to donate is left up to the individual although donation is highly supported by the denomination.

Baptist

Though Baptists generally believe that organ and tissue donation and transplantation are ultimately matters of personal conscience, the Nation's largest Protestant denomination, the Southern Baptist Convention, adopted a resolution in 1988 encouraging physicians to request organ donation in appropriate circumstances and to "encourage voluntarism regarding organ donations in the spirit of stewardship, compassion for the needs of others and alleviating suffering." Other Baptist groups have supported organ and tissue donation as an act of charity and leave the decision to donate up to the individual.

Buddhism

Buddhists believe that organ donation is a matter that should be left to an individual's conscience. Reverend Gyomay Masao Kubose, president and founder of The Buddhist Temple of Chicago and a practicing minister, says, "We honor those people who donate their bodies and organs to the advancement of medical science and to saving lives." The importance of letting loved ones know your wishes is stressed.

Catholicism

Catholics view organ donation as an act of charity, fraternal love, and self-sacrifice. Transplants are ethically and morally acceptable to the Vatican. Pope John Paul II stated, "The Catholic Church would promote the fact that there is a need for organ donors and that Christians should accept this as a 'challenge to their generosity and fraternal love' so long as ethical principles are followed."

Christian Church (Disciples of Christ)

This church encourages organ and tissue donation, stating that people were created for God's glory and for sharing God's love. A 1985 resolution adopted by the General Assembly encourages "members of the Christian Church (Disciples of Christ) to enroll as organ donors and prayerfully support those who have received an organ transplant."

The Church of Christ, Scientist

Christian Scientists do not take a specific position on transplants or organ donation. They normally rely on spiritual, rather than medical, means for healing. Organ and tissue donation is an issue that is left to the individual church member.

Episcopal

The Episcopal Church recognizes the life-giving benefits of organ, blood, and tissue donation. All Christians are encouraged to become organ, blood, and tissue donors as "part of their ministry to others in the name of Christ, who gave His life that we may have life in its fullness."

Greek Orthodox

According to Reverend Dr. Milton Efthimiou, Director of the Department of Church and Society for the Greek Orthodox Church of North and South America, "The Greek Orthodox Church is not opposed to organ donation as long as the organs and tissue in question are used to better human life, i.e., for transplantation or for research that will lead to improvements in the treatment and prevention of disease."

Gypsies

Gypsies tend to be against organ donation. Although they have no formal resolution, their opposition is associated with their belief in the afterlife. Gypsies believe that for 1 year after a person dies, the soul retraces its steps. All parts of the body must remain intact because the soul maintains a physical shape.

Hinduism

Hindus are not prohibited by religious law from donating their organs according to the Hindu Temple Society of North America. In fact, Hindu mythology includes stories in which parts of the human body are used for the benefit of other humans and society. The act is an individual decision.

Independent Conservative Evangelical

Generally, Evangelicals have had no opposition to organ and tissue donation. Donation is an individual decision.

Islam

Muslims believe in the principle of saving human lives and permit organ transplants as a means of achieving that end.

Jehovah's Witnesses

Jehovah's Witnesses believe donation is a matter best left to an individual's conscience. All organs and tissue, however, must be completely drained of blood before transplantation.

Judaism

All four branches of Judaism (Orthodox, Conservative, Reform, and Reconstructionist) support and encourage donation. Said Orthodox Rabbi Moses Tendler, "if one is in the position to donate an organ to save another's life, it's obligatory to do so, even if the donor never knows who the beneficiary will be. The basic principle of Jewish ethics – 'the infinite worth of the human being' -- also includes donation of corneas, since eyesight restoration is considered a life-saving operation." In 1991, the Rabbinical Council of America (Orthodox) approved organ donations as permissible and even required, from brain-dead patients. The reform movement looks upon the transplant program favorably. Rabbi Richard Address, Director of the Union of American Hebrew Congregations Bio-Ethics Committee, stated that, "Judaic Responsa materials provide a positive approach and by and large the North American Reform Jewish community approves of transplantation."

Lutheran

In 1984, the Lutheran Church in America passed a resolution stating that donation contributes to the well-being of humanity and can be an “expression of sacrificial love for a neighbor in need.” They call on members to consider donating organs and to make any necessary family and legal arrangements, including the use of a signed donor card.

Mennonite

Mennonites have no formal position on donation but are not opposed to it. They leave the decision to the individual or his/her family.

Moravian

The Moravian Church has made no statement addressing organ and tissue donation or transplantation. Robert E. Sawyer, President, Provincial Elders Conference, Moravian Church of America, Southern Province, states, “There is nothing in our doctrine or policy that would prevent a Moravian pastor from assisting a family in making a decision to donate or not to donate an organ.” It is, therefore, a matter of individual choice.

Mormons

The Church of Jesus Christ of Latter-Day Saints considers the decision to donate organs a selfless act that often results in great benefit, and the decision to donate for medical purposes or the decision to authorize donation from a deceased family member is made by the individual or deceased member’s family. The church states that the decision should be made after receiving competent medical counsel and confirmation through prayer.

Pentecostal

Pentecostals leave the decision to donate up to the individual.

Presbyterian

Presbyterians encourage and endorse donation. It is an individual’s right to make decisions regarding his or her own body.

Seventh-Day Adventist

Donation and transplantation are strongly encouraged. Seventh-Day Adventists have many transplant hospitals, including Loma Linda in California, which specializes in pediatric heart transplantation.

Shinto

In Shinto, the dead body is considered impure and dangerous and thus quite powerful. Injuring a dead body is a serious crime. It is difficult to obtain consent from bereaved families for organ donation or dissection for medical education or pathological anatomy because Shintos relate donation to injuring a dead body. Families are concerned that they not injure the *itai*, the relationship between the dead person and the bereaved people.

Society of Friends (Quakers)

Quakers do not have an official position. They believe that organ and tissue donation is an individual decision.

Unitarian Universalist

Organ and tissue donation is widely supported by Unitarian Universalists. They view it as an act of love and selfless giving.

United Church of Christ

Reverend Jay Lintner stated, “United Church of Christ people, churches and agencies are extremely and overwhelmingly supportive of organ sharing. The General Synod has never spoken to this issue because, in general, the Synod speaks on more controversial issues, and there is no controversy about organ sharing, just as there is no controversy about blood donation in the denomination. While the General Synod has never spoken about blood donation, blood donation rooms have been set up at several General Synods. Similarly, any organized effort to get the General Synod delegates or individual churches to sign organ donation cards would meet with generally positive responses.”

United Methodist

The United Methodist Church issued a policy statement regarding organ and tissue donation. In it, they state that “The United Methodist Church recognizes the life-giving benefits of organ and tissue donation, and thereby encourages all Christians to become organ and tissue donors by signing and carrying cards or driver's licenses, attesting to their commitment of such organs upon their death, to those in need, as a part of their ministry to others in the name of Christ, who gave his life that we might have life in its fullness.” A 1992 resolution states, “Donation is to be encouraged, assuming appropriate safeguards against hastening death and determination of death by reliable criteria.” The resolution further states, “Pastoral-care persons should be willing to explore these options as a normal part of conversation with patients and their families.”

GLOSSARY OF TERMS AND ACRONYMS

Glossary of Terms

Agonal factors. Physiologic variables related to agonal state that may or may not have an effect and/or relation to quality of postmortem tissues.

Agonal state. The state of an individual during the time immediately preceding death.

Allograft. Tissue recovered from one individual for transplantation into another individual.

Authorization. Approval typically given by NOK for postmortem tissue donation.

Call center. A dedicated phone center typically available at all times that has been established to obtain consent and coordinate recovery for organ and tissue donation for transplant and/or research.

Cause(s) of death. The underlying cause of death, which can be defined as (a) all diseases, morbid conditions, or injuries that either resulted in or contributed to death or(b) the circumstances of the accident or violence that produced any such injuries.

Cold ischemia time. In surgery, the time between the chilling of a tissue, organ, or body part after its blood supply has been reduced or cut off and the time it is warmed by having its blood supply restored. This can occur while the organ is still in the body or after it is removed from the body if the organ is to be used for transplantation.

Comparator tissue. A tissue sample that can be used for comparison to another to address a research questions; example: normal liver (comparator tissue) versus diabetic liver.

Control tissue. A tissue sample used as a point of comparison with another to address a research question.

Donation after cardiac death (DCD). Tissue donation from donors who are declared deceased on the basis of cardiopulmonary criteria (irreversible cessation of circulatory and respiratory function) and who have a very small chance of recovery. This condition is distinguished from donation after brain death, as DCD donors do not meet neurologic criteria for brain death.

Donation service area. The geographic area across which an OPO or TRO accepts donations and organizes recoveries.

Donor identification. The process of screening and confirming eligibility of a potential organ and/or tissue donor candidate.

Donor notification. The process by which a hospital, hospice, funeral home, or ME notifies a call center for donor screening and consent in the event of a death and/or a family's wish to donate.

Donor recruitment. The process of approaching individuals to educate them on the value or organ donation in the hope that they will provide (antemortem) consent for donation for transplant and/or research.

Evidence-based biobanking. The process of integrating data-driven scientific evidence from biospecimen analyses into the daily operation of biospecimen resources and related research procedures to improve quality and overall research efficiency.

Extended criteria donor. Donors who are 60 years of age and older or donors ages 50 to 59 years with comorbidities who are candidates for tissue donation.

Hardy Scale. A four-point scale aimed at categorizing death based on related agonal factors to predict research tissue quality (see section C5, table 1 for listing).

Iatrogenic effects. Conditions that may affect tissue quality that are induced inadvertently on a patient or donor by a physician, surgeon, medical treatment, or diagnostic procedure.

Informed consent. Consent given by a patient or authorized individual for a medical procedure or participation in a clinical study after achieving an understanding of the relevant medical facts and the risks involved.

Next-of-kin. The person(s) who is/are most closely related to a donor and who would be approached for authorization / consent to donate.

Organ procurement organization. A certified, not-for-profit organization designated to be responsible for the procurement of organs for transplantation and the promotion of organ donation within a given donation service area.

Pathological review. An assessment of the gross (macroscopic) and/or microscopic features of an organ or tissue sample to determine the presence or absence of disease.

Postmortem donor. An individual from whom tissues and/or organs are acquired for postmortem transplant and/or research are acquired.

Postmortem interval. The time elapsed since a person has died.

Presumed/implicit consent. A policy of granting authority to healthcare personnel to perform procedures or to remove organs for transplantation from deceased individuals unless an objection is registered by family members or by the patient prior to death.

Rapid autopsy. An autopsy performed soon after death for diagnostic purposes or for collection of tissues for research. Rapid autopsy is sometimes referred to as “warm” autopsy.

Recovery team. Trained and dedicated staff and experts who procure, process, and recover human tissues postmortem.

Standard criteria donor. Donors up to 60 years of age with no comorbidities who are candidates for tissue donation.

Time of death. The time that clinical, cardiac, and brain death are confirmed by the appropriate medical party.

Tissue broker. An organization that aims to match researchers’ requests with appropriate donated tissue.

Tissue processors. Industrial and biotechnology organizations that process and refine human tissues for clinical applications and applied research to support research and improve human health and quality of life.

Warm ischemia time. The time that a tissue, organ, or body part remains at body temperature after its blood supply has been reduced or cut off but before it is cooled or reconnected to a blood supply.

Warm autopsy. See Rapid Autopsy.

Whole-body donor. An individual whose entire body has been donated after death for medical research and education.

Acronyms

AATB	American Association of Tissue Banks
ABO	Blood typing
AOPO	American Association of Organ Procurement Organizations
caHUB	cancer Human Biobank
caBIG	cancer Biomedical Informatics Grid
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CMS	Centers for Medicare & Medicaid Services
CRF	Case report form
DCD	Donation after cardiac death
FDA	U.S. Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
cGTP	current Good Tissue Practices
HBV	hepatitis B virus
HCV	hepatitis C virus
H&E	hematoxylin and eosin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HTLV	human T-lymphotropic virus
IRB	institutional review board
LSA	last seen alive
ME	medical examiner
MTA	material transfer agreement
NIMH	National Institute of Mental Health
NCI	National Cancer Institute
NDFC	National Donor Family Council
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NOK	Next-of-kin
NOTA	National Organ Transplant Act
OBRR	Office of Biorepositories and Biospecimen Research
OBRA	Omnibus Budget Reconciliation Act
OCT	optimum cutting temperature compound
OPO	organ procurement organization
OPTN	Organ Procurement and Transplant Network
PI	principal investigator
QA	quality assurance
QC	quality control
RAP	rapid autopsy program
RIN	RNA integrity number

RUAGA	Revised Uniform Anatomical Gift Act
SPORE	Specialized Program of Research Excellence
SOP	standard operating procedure
TRO	Tissue recovery organization
UAGA	Uniform Anatomical Gift Act
UNOS	United Network for Organ Sharing

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