



NCI Best Practices for Biospecimen Resources

Biorepositories and Biospecimen Research Branch

National Cancer Institute

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INTRODUCTION

Unprecedented advances in biomolecular technology have greatly increased the power and precision of analytical tools used in cancer research and have accelerated the drive toward personalized medicine. Human specimens that are analyzed using these new and developing technology platforms have emerged as a critical resource for basic and translational cancer research because they are a direct source of molecular data from which targets for therapy, detection, and prevention are identified and molecular taxonomies of cancer are derived. The reliability of molecular data derived from these new analysis platforms is dependent on the quality and consistency of the biospecimens being analyzed. As a result of the increased requirement for biospecimen quality, standardization of biospecimen resources using state-of-the-science approaches has become a pressing need across the research enterprise. The lack of standardized, high-quality biospecimens is widely recognized as a significant roadblock to cancer research.

Over the past several years, the National Cancer Institute (NCI) has undertaken an intensive due-diligence process to understand the state of its funded biospecimen resources and the quality of biospecimens used in cancer research. The *NCI Best Practices for Biospecimen Resources (NCI Best Practices)* were first published and released in June 2007. The *Best Practices* were again revised in 2011 and posted on the NCI Biorepositories and Biospecimen Research Branch (BBRB) web site [1]. Major revisions in 2011 included: the addition of new sections on [biospecimen resource management and operations](#) and [conflicts of interest \(COIs\)](#); expansion of recommendations related to [custodianship](#) and [informed consent](#) based on the consensus findings of the 2007 NCI-hosted Symposium-Workshop on Custodianship and Ownership Issues in Biospecimen Research; updating and addition of more current references; and harmonization with current Federal guidance documents and recommendations from international biospecimen organizations.

This revised 2016 version of the *NCI Best Practices* is intended to provide more current and detailed recommendations related to biospecimen and data quality. This version includes updates and revisions as follows;

- Section B, Technical and Operational Best Practices, has updated internet references, updated recommendations based on more recent research, guidance and standards for collecting, processing and storing specimens; updated (Sections B.5, B.6) informatics practices in recognition of the phasing out of the caBIG and caGRID programs; and updated literature references.
- Section C, Ethical, Legal and Policy Practices, has been updated based on more recent guidance concerning informed consent for genomics research; return of research results, and incidental findings; community engagement; and corrections and updates to internet references.

The *NCI Best Practices* identifies salient guiding principles that define state-of-the-science biospecimen resource practices, promotes biospecimen and data quality, and supports adherence to ethical and legal requirements. The current *NCI Best Practices* does not comprise detailed laboratory procedures; rather, the document consists of principles by which such procedures should be developed by biospecimen resources. Many of the principles have been adopted, in whole or in part, by accrediting programs for biorepositories, such as the Biorepository Accreditation Program of the College of American Pathologists (College of American Pathologists, or CAP [2]). Organizations contemplating an application for accreditation by CAP or other entities will find careful review of the *Best Practices* a helpful starting point in evaluating biospecimen resource practices and administrative oversight. The recommendations contained within this document are intended to be adapted, as appropriate, based on the mission and scientific needs of individual biospecimen resources. Although adoption of the *NCI Best Practices* is voluntary, the NCI believes that the principles outlined in this document support the goal of optimizing biospecimens for cancer research.

The *NCI Best Practices* will continue to evolve as the field of biospecimen science advances; novel scientific, technological, and clinical practices develop; and new ethical and legal policies and regulations emerge. Results from biospecimen research initiatives such as those from the NCI Biospecimen Research Network (BRN) [3-

[11](#)] will continue to inform future versions of the *NCI Best Practices* as the community moves toward the development of biospecimen evidence-based practices [\[12\]](#) and standard operating procedures (SOPs) that are both biospecimen-type specific and analysis platform specific. The NCI is committed to maintaining current and scientifically accurate best practices for biospecimen resources and will continue to solicit input from stakeholders in the cancer research community.

NATIONAL CANCER INSTITUTE BEST PRACTICES FOR BIOSPECIMEN RESOURCES

A. Scope, Applicability, and Implementation

A.1. Scope

This document identifies technical; operational; and ethical, legal, and policy best practices in order to ensure a level of consistency and standardization across biospecimen resources¹. A biospecimen resource is defined as a collection of human specimens and associated data for research purposes, the physical structure where the collection is stored, and all associated processes and policies. Biospecimen resources vary considerably, ranging from formal organizations to informal collections of materials in an individual researcher's freezer. The NCI chose to use the term biospecimen resource to encompass both the physical structure and the policies and procedures which are associated with such resources.

A.2. Applicability and Implementation

The *NCI Best Practices* are intended to be applicable to all biospecimen resources. The implementation of the *NCI Best Practices* is voluntary, and several recommendations in the *NCI Best Practices* can be broadly or narrowly applied depending on the mission of the biospecimen resource and/or the study design. Biospecimen resource managers are encouraged to implement the *NCI Best Practices* in their biospecimen management plans as appropriate. The NCI will continue to develop tools and resources to assist in implementation of the *NCI Best Practices*.

A.3. Format of the *NCI Best Practices*

In this version, implementation of the *NCI Best Practices* will continue to be facilitated via an online format. The online format provides a mechanism for more frequent updates and includes additional resources and tools to assist the biospecimen resource community in implementation of the *NCI Best Practices*.

B. Technical and Operational Best Practices

B.1. Biospecimen Resource Management and Operations

Daily and long-term responsibilities essential for efficient biospecimen resource management and operations can be diverse and include organizational considerations, space planning and functional design, resource development, evaluation and solidification of infrastructure requirements, constant and consistent review of operational issues, and regular resource evaluation. When executed and practiced in harmony, all of these factors can dramatically improve success in managing and operating a high-quality, highly utilized, and valuable resource.

B.1.1. Organizational Overview of the Biospecimen Resource

An organizational overview can assist in defining the institutional structural components within and around the biospecimen resource. An overview typically begins with description of the organizational mandate; its associated goals, mission, and vision; operational scope; and core areas of research support.

¹ The term biospecimen resource is used to define more broadly the facilities, policies and procedures which are often referred to as biobanks or biorepositories.

B.1.1.1. Organizational Structure

Organizational structures may vary according to the nature of the biospecimen resource. Thoughtful documentation of the resource's organizational structure in relation to its parent institution may help to predict needs, promote incorporation of existing resources, and streamline workflow while increasing communication among stakeholders, management, and end users.

- Biospecimen resources should seek to define and document their organizational structure in advance of resource planning and/or development.

B.1.1.2. Organizational Chart

The organizational chart can be a significant tool in supporting existing governance structures through elucidation of roles, responsibilities, chain of command, and requisite reporting relationships.

- Biospecimen resources should develop and publicly display the current organizational chart within the resource.
- Biospecimen resource management should provide a copy of the current organizational chart and discuss with every new staff member as part of the orientation process, reviewing the current management of the institution ([Appendix 3](#)).

B.1.2. Biospecimen Resource Personnel

Personnel involved in biospecimen resource management and use, including researchers, technicians, nurses, surgeons, pathologists, anesthesiologists, and assistants should be aware of the purpose and goals of the biospecimen resource (see [Section B.1.2.1](#), Related Personnel Descriptions and Roles). To ensure the collection of high-quality biospecimens for research, personnel should be well qualified and trained to adhere to applicable SOPs. See the BBRB web site [\[13\]](#) and the NCI Biospecimen Research Database [\[14\]](#) for examples of SOPs which can be adapted by biospecimen resources for their own applications [\[12\]](#).

Updated training of personnel should be conducted on a periodic basis, in accordance with applicable regulations and position descriptions [\[15\]](#). A pathologist or his/her designee—such as a pathology assistant or another individual with applicable training and judgment—should be involved in collecting and processing anatomical pathology biospecimens, including surgical and autopsy tissue and body fluids. It is important that a pathologist determines which biospecimen, or portion thereof, is necessary for complete evaluation and which is excess (remnant tissue) that may be provided to the biospecimen resource for research purposes. The involvement of a pathologist in this process is crucial in order to ensure that patient care is not compromised.

B.1.2.1. Related Personnel Descriptions and Roles

The following general personnel categories may be useful in biospecimen resource planning. Note that these personnel and groupings may not be applicable to smaller biospecimen resources.

- Stakeholders and Governance Team: Stakeholders may include leaders at institutional cancer centers and pathology, surgery, and bioinformatics departments and leaders in clinical research units, translational research, and epidemiology teams. Patient advocates and research participants are also key stakeholders.
- Biospecimen Resource Management Team: Typically consists of a director, associate director, technical director, and director of quality management.
- Adjunct Research Support Teams: May include clinical research coordinators and study nurses, research assistants, laboratory technicians, bioinformatics professionals, clinical residents and fellows, and statisticians.
- Internal Support System: May include space planning, financial administration, comptroller, purchasing, environmental services/maintenance, telecommunications, informatics and marketing.

- External Support/Outsourced Roles: May include vendors, consultants, contractors, architects, and engineers.

B.1.2.2. Oversight Committees

Oversight committees, often composed of experts from outside the biospecimen resource, serve to oversee the resource and support transparent and accountable operations. Care should be taken to define, evaluate, and document any potential conflicts of interests ([COIs](#)) for any and all members. The type of oversight committee(s) needed at each biospecimen resource will vary but may include the following:

- Scientific Advisory Committee: Provides strategic guidance, scientific feedback, and advice on resource development to the biospecimen resource management and stakeholders.
- Biospecimen Use (or Access) Committee: Supports access to biospecimens for research through assessment of criteria such as scientific rationale, validity of the scientific project, regulatory adherence, potential conflicts of interest, and fair biospecimen/data allocation practices.

B.1.2.3. Associated Institutional Offices and Adjunct Committees and Their Roles

Institutional offices and committees play a supporting governance role for biospecimen resources. Such offices can offer tremendous expertise along with essential support for the internal resource and its collaborators.

Examples of associated offices include but may not be limited to the following:

- Office of Regulatory Affairs: Typically established to aid regulatory review and oversight of research protocols.
- Office of Human Subjects Research: Typically performs an auditing function for clinical research trials and related research support centers.
- Office of Research Services: Grant management support and assistance with contract development.
- Technology and Materials Transfer Office: Assists with [material transfer agreement](#) (MTA) development and management.
- Legal Affairs: Offers guidance on relevant case law, aids in contractual negotiations and/or disputes.
- Office of Environmental Health and Radiation Safety: Offers advice on biosafety but may also consult concerning resource development and/or expansion.

Additional supporting adjunct committees may include a Clinical Trials Scientific Review and Monitoring Committee, which provides supplemental regulatory, data privacy, and safety review in parallel with the institutional review board (IRB).

B.1.3. Considerations Related to Planning and Development

Consideration of the biospecimen resource mission, operational scope, and objectives is crucial in execution of all stages of the planning process. For startup resources, initial operational planning and developmental considerations should aim to include establishment of a governance structure as well as development of related policy, along with regulatory and procedural standards. Once the foundation is set in place, the next step is to commence biobanking protocol, procedural, and formal business development. For biospecimen resources that function as core facilities and/or service providers, business planning may include financial and cost-recovery modeling. In 2014 BBRB coordinated two such biobanking economics studies through a series of comprehensive surveys, and the development of a web-based planning tool, the Biobank Economic Modeling Tool (BEMT) [[16](#)]. The BEMT will aid in better understanding and planning for the true costs of biobanking. Reconsideration of these issues may also be timely for established resources, particularly to address any operational disparities in an effort to support best practices and promote long-term sustainability [[17-20](#)].

B.1.3.1 Oversight, Internal Policy, and Procedure Development

Policy development can be crucial to provide a framework to guide operations.

- Biospecimen resources should define, document, and observe policies in alignment with the resource mission, scope, and operational objectives.
- All resource policies should undergo a standardized, documented vetting and approval process.

B.1.3.2. Determination of Procedural and Regulatory Standards

During resource development it can be helpful to review current procedural and regulatory standards and determine which are pertinent to the resource operations.

Biospecimen resource managers should aim to:

- Familiarize themselves with the current best practice documents to determine initial base standards for resource development, operations, management, evaluation, and expansion.
- Orient staff and adjunct teams to current best practice documents and published standards.
- Incorporate best practices and current relevant standards into resource policies, SOPs, and procedures with an emphasis on supporting evidence-based practices ([[12](#), [14](#)], [Appendix 5](#)).

B.1.3.3. Business Planning

Business planning can provide justification for financial and institutional commitment and quantification of startup and sustainability costs [[17-21](#)].

- Business planning should be integrated into all aspects of operations, biospecimen resource management, and evaluation.
- Resources should aim to establish a documented annual business plan developed with department staff input and aligned with the vision and mission of the resource. Business plan items should be specific, measurable, actionable, relevant, and time bound.
- The resource business plan should also include a formal continuity plan that addresses all possible operational disruptions, including disaster planning.
- If the resource functions as a service center, the business plan should address issues related to service and revenue generation.

B.1.4. Biospecimen Resource Infrastructure and Space Planning

When planning, it is crucial to fully assess startup, operational, and maintenance costs for any and all infrastructure [[21](#), [22](#)]. Some favor a centralized model in an attempt to promote harmonization to achieve standardized, well-annotated, high-quality, robust biospecimen and data repositories. In this regard, it can be helpful for each institution to perform evaluative exercises, for example using the ISBER Self-Assessment Tool [[23](#)].

Infrastructure requirements can vary based on the biospecimen resource scope and requirements. Infrastructure requirements include but are not limited to the physical laboratory, office, and adjunct and/or satellite space needs as well as requisite informatics, equipment, storage platforms, telecommunications, and consumables needs.

In general, the baseline requirements should aim to include ample space for the following functions, where appropriate, based on the nature and functions of the resource:

- Collection, receiving, tracking, and shipping as needed.
- Immediate and interim processing (e.g., fine and gross dissection benches).
- Areas to prepare and process blood products.

- Histological preparation.
- Equipment such as safety hoods (laminar flow), centrifuges, freezers.
- Stations for pathology case review.
- Storage for biospecimens, consumables, and related records.
- Office work areas to support data, operational, and end user management.

In addition, some biospecimen resources may include areas dedicated to purification of nucleic acids, tissue and cell culture, single-cell suspension, and other specialized laboratory practices.

B.1.5. Overall Operational Considerations

B.1.5.1. Equipment Selection and Maintenance

Equipment selection complements infrastructure planning and should be considered in parallel with space planning and resource design.

Biospecimen resource management should:

- Consider the following factors when selecting equipment: Current resources and budget, current and future services, need, frequency of use, vendor options, manufacturing lead time, and cost—including maintenance, delivery, warranty, service contracts, lifespan, eco-friendliness, performance, and efficiency cost savings, along with current and future service provision options.
- Aim to factor depreciation for all capital equipment into the cost-recovery plan when appropriate.
- Utilize resource sharing to defray financial investment in equipment.
- Determine if used/sale equipment is appropriate.
- Consider batching service contracts among neighboring resources to save money.
- Review calibration and validation instructions.
- Review preventive maintenance summaries and/or equipment log files after and prior to scheduling all maintenance visits as part of the quality assurance program.

B.1.5.2. Purchasing and Procurement from Vendors

Familiarity with purchasing as well as the overall procurement process can help support best practices; decrease errors in purchasing and product selection; streamline workflow; decrease lags in ordering/purchasing; and increase awareness of institutional documentation requirements, purchasing limitations, and rules. When possible, evaluating multiple vendors for equivalency will reduce the impact to business continuity, for example, if a vendor needs to be replaced or augmented.

B.1.5.3. Project Management

Proactive project management can ensure quality service provision and promote a smooth, efficient operational workflow while avoiding duplication of effort and resources.

When possible, biospecimen resources should:

- Utilize a project management plan that includes, but may not be limited to, a statement of work, deliverables document, and integrated project plan (as needed) for facility-managed projects.

B.1.5.4. Biospecimen Utilization

Biospecimen utilization is the process of biospecimen management in an effort to promote collaboration and timely research.

Biospecimen resources should aim to:

- Assess biospecimen utilization in a timely and efficient manner.
- Document and track utilization in conjunction with the resource inventory management system.
- Share information about their biospecimens to the external community through a biospecimen management information system or other means. One method to publicize basic information about sharable biospecimens is via the NCI Specimen Resource Locator [24] ([Section B.6.3](#), Interoperability). Additional information about specimen resources may be found on the ISBER web site [25].

B.1.6. Biospecimen Resource Evaluation and Assessment

The evaluation process can be a valuable exercise to aid executive decision-making with respect to assessment of future funding needs, overall service quality and effectiveness, customer satisfaction, program results, scientific and financial impact, opportunities for expansion, crucial lessons learned, and program success.

Evaluation should include the following general topic areas:

B.1.6.1. Self-Auditing, Audit Preparedness, and Clinical Research Monitoring

Self-auditing and audit preparedness are cornerstones to support and/or evaluate areas of poor performance as well as success in quality of operations. Audits and surveys may be conducted in relation to monitoring of end-user support for clinical biobanking efforts.

B.1.6.2. Strategic and Long-Range Planning, Setting Benchmarks

Strategic and long-range planning can help to set a resource roadmap, provide opportunities to fine-tune and reset operational focus, offer proof of concept, provide analysis of resource allocation, highlight crucial lessons learned, accelerate decision making and resource growth, and increase communication and understanding of resource benefits.

B.1.6.3. Quantification of Performance, Utilization Review, and Assessment of Continuing Research Needs of the Resource

Formal quantification of performance justifies the benefit, utility, and overall need for the stakeholder's financial investment in the biospecimen resource. BBRB's BEMT is designed to support cost recovery and financial planning for biobanks [16].

B.1.6.4. Scientific Impact of the Resource

Formal analysis of scientific impact can provide evidence of the inherent and extrinsic scientific value and contribution of the resource. Proponents of such impact analyses have published guidelines (Biospecimen Resource Impact Factor [26]), but it is not expected that many biospecimen resources will have the financial resources or information they would need to conduct such a self-assessment, except as noted through the ISBER Self-Assessment Tool.

B.2. Biospecimen Collection, Processing, Storage, Retrieval, and Dissemination

The aim of every biospecimen resource should be to collect, maintain, and disseminate the highest quality biospecimens, based on the intended research use. High-quality biospecimens are defined as those whose biology most closely resembles the biology of the biospecimen prior to its removal from the human research participant. Once the biospecimen is collected (and sometimes prior to its removal) the biospecimen may begin to take on new characteristics based on changes to the biospecimen's environment; e.g., changes in exposure to certain nutritional, chemical, or other environmental factors that may occur during a surgical or collection procedure [4-11]. Such changes may result in inaccurate determinations of the molecular and physical

characteristics of the biospecimen during subsequent analysis. Every attempt should be made to minimize the effects of biospecimen handling on biospecimen integrity.

Note that guidance provided in this section is intended for application when planning for biospecimen collection, processing, and storage, prior to the initiation of the collection efforts. Note that study design will also inform whether certain pre-analytical factors can be controlled and data collected as described below.

B.2.1. Pre-Analytic and Analytic Variables

A variety of factors may affect biospecimen quality and research results; these may be divided into two general categories designated “pre-analytic factors” and “analytic factors.” Pre-analytic factors refer to collection, processing and storage variations that influence biospecimen integrity prior to its removal from the human research participant and carry through to the point at which a biological specimen is ready for testing. Analytic factors refer to those variations that affect performance of a particular testing procedure [8, 27, 28].

The scientific study of biospecimen pre-analytic factors and their effects on molecular integrity is known as Biospecimen Science. Systematic studies in Biospecimen Science have been sponsored and conducted by programs such as the NCI’s BRN [3], and the Standardisation and improvement of generic Pre-analytical tools and procedures for In-vitro **DI**Agnostics project (SPIDIA) [29], a consortium that was funded by the European Union and coordinated by QIAGEN in Germany. The aim of these programs is to identify the major questions of biospecimen methodology and pre-analytic factors, conduct original research to address these questions, and develop evidence-based practices to guide new biospecimen collections and mitigate pre-analytic effects when collecting and utilizing stored biospecimens. Both the BRN and SPIDIA initiatives have resulted in significant findings which have advanced the field of biospecimen science and promoted best practices for biospecimen use in clinical and basic research programs [4-11, 30-32].

B.2.1.1. Pre-Analytic Factors

Pre-analytic variables may be divided into three general areas:

- The physiology of the human research participant prior to biospecimen collection;
- Biospecimen collection practices; and
- Biospecimen handling practices prior to their inclusion in downstream testing ([Appendix 5](#), Example of Biospecimen Evidence-based Practice); [4-11]

B.2.1.1.1. Physiology of the Human Research Participant. Research has demonstrated that analyte levels may be affected by a variety of factors such as the overall health of the human research participant, the type of anesthesia used, food and beverages consumed prior to biospecimen collection, the medication status of the patient, and the time of day at which the biospecimen was collected [33, 34]. Additionally, the menstrual cycle in females may affect some downstream analyses. Efforts should be made to collect and record information pertaining to these factors to decrease or adjust for the variability of these contributing factors. The issue of medications is particularly important since many over-the-counter medicines may not be remembered as such by the patient (antacids, non-steroidal anti-inflammatory medications, for example).

B.2.1.1.2. Uniformity in Biospecimen Collection Practices. The methods used to remove and collect biospecimens from human research participants may influence the quality of the biospecimens collected. Significant research has indicated that during surgical removal of biospecimens the amount of time following the cessation of blood flow to an organ can affect both levels and molecular profiles of target analytes [5, 35-37]. The biospecimen should be preserved as quickly as possible after removal from the patient; e.g., appropriately sized tissue sections snap frozen and/or placed into 10 percent phosphate-

buffered formalin, as appropriate. In recent years alternative fixatives have been developed and validated, such as PaxGene Tissue®, which allows for the preservation of tissue for molecular analysis as well as histological analysis [38]. As appropriate, consideration should be given to the use of newer preservation methods. Expected as well as unforeseen future uses of biospecimens should be considered when deciding on preservation methods. When biospecimens are collected from research participants, the organ site at which the biospecimen is removed (tumor or non-tumor, as well as location within the tumor), any anesthetic being used, warm ischemia time (the length of time the specimen is only partially perfused due to vessel ligation during surgery, before complete removal), any stabilizing agents used to preserve the biospecimen following its removal, the type of fixatives used and the length of time the tissues are exposed to fixatives, any further processing, and the temperature at which biospecimens are maintained following collection (as well as duration i.e. cold ischemia time) may all affect molecular stability and degradation. The NCI maintains a publicly available, online database that collates the published literature on these and other pre-analytical factors: the Biospecimen Research Database [14].

Prior to the collection or removal of biospecimens, a plan should be in place to allow for the appropriate annotation of the biospecimens. This annotation should include information about the human research participant as noted in Section B.2.1.1.1 above, and timing of collection and processing activities; e.g., the type of clearing agent, the type and temperature of paraffin used to process the biospecimen, etc. [15]. These data should be maintained in a database that can be linked to the biospecimen at all times (see Section B.5, Collecting and Managing Clinical Data, and Section B.6, Biospecimen Resource Informatics). Details about particular biospecimen collection, processing, and storage procedures can be important supporting information for scientific publications on research utilizing the biospecimens [39]. NCI, with an international committee, published a set of recommendations for reporting the conditions of biospecimen collection, processing, and storage procedures. These recommendations, known as BRISQ (Biospecimen Reporting for Improved Study Quality), have been adopted by several scientific journals and are mentioned in the *Nature* guidelines for authors [39-42].

B.2.1.1.3. Biospecimen Handling Procedures. Every attempt should be made to optimize the handling of biospecimens to minimize molecular changes that may result from the processing activities, most critically by reducing cold ischemia time (the time the biospecimen spends after complete removal from the patient but before being placed into fixative). Other critical factors include the temperature and timing of biospecimen processing, the size and volume of the biospecimens that will be stored for future use, and the number of aliquots to be prepared from each biospecimen. Multiple small aliquots allow for analysis or experimentation on one specimen, while minimizing freeze-thaw degradation of other stored samples ([43] CAP Biorepository Accreditation Program Requirement (Appendix 6, BAP.01900)). When samples are stored in a frozen state, the rate at which they are cooled to the storage temperature can influence the rate at which molecular degradation occurs, and subsequent freeze-thaw cycles can further degrade the molecular integrity of the biospecimens. Tracking of temperature excursions is recommended, and required by accrediting organizations ([43] BAP.02000).

B.2.1.2. Analytic Factors

When pre-analytical variables are introduced they lead to differences in the performance of a particular assay. To minimize errors in assay reproducibility, the following considerations should be applied:

- Use of validated assays, where possible;
- Use of SOPs in which the technical staff are well-trained;
- Lot uniformity of reagents;
- Inclusion of appropriate type and number of quality control (reference) samples;
- Randomization, when possible; and
- Standardized methods for documenting and interpreting testing results.

B.2.2. Determining Which Biospecimens to Collect

The specific mission and goals of a biospecimen resource will influence the type of biospecimens collected. The biospecimens collected should be appropriate and feasible for the clinical setting, as well as appropriate for the downstream applications anticipated for the biospecimen. If tissue specimens are being collected, they should be reviewed histologically for accuracy by a qualified histopathologist; this is a requirement for some accrediting agencies ([43] [BAP.02500](#)).

B.2.3. Defining Reference Ranges

Aside from pre- and analytic factors, research dictates that values for particular cellular analytes are more accurately represented by a normal biological range of values (or reference range), even among individuals characterized as “normal” or “healthy.” Disease is defined as a distinct deviation from the range of normal variation, and diagnosis of disease depends on knowing the scope of boundaries of normal variation. Where possible, efforts should be made to characterize reference ranges for the analyte of interest in the biospecimen of interest to ensure the likelihood of accurately detecting any deviation from the reference range.

B.2.4. Requirement for Evidence-Based Standard Operating Procedures

To have confidence in research results, it is critical that all reagents be fit-for-purpose and quality-controlled for use in the assay. SOPs should be reproducible with standard reference material (where possible), and control biospecimens that provide a range of anticipated assay values should be utilized; this is a requirement for accrediting organizations ([43] [BAP.01000](#), [BAP.01500](#)). Biospecimens that have been poorly handled are likely to provide erroneous test results because of the molecular changes resulting from the handling process.

A model for constructing and annotating biospecimen evidence-based practices has been published by the NCI [12] and is publicly available at the BBRB web site [44].

It is impractical and currently not possible to consider the development of assays to measure the stability of every cellular component within a biospecimen. To that effect, protocols that optimize the general stability of biomolecules under certain environmental conditions are recommended [15]. Should a particular biomolecule be of interest, it is important to perform some type of analysis to ensure that the storage and handling conditions implemented will allow for accurate determinations of that biomolecule.

B.2.5. Methods Research

All research endeavors should be based on well-characterized and validated assays, where possible [45]. Even assays that are developmental in nature should be tested to ensure that they are reproducible over time. “Proof of Performance” tests [15] allow for testing replicate samples over time to allow for measurement of standard deviations in the assays performed.

Where possible, research should be performed to ensure that the storage and handling procedures implemented are ones that will be conducive to stabilization of the molecular components and particular targets of interest within the biospecimen.

B.2.6. Biospecimen Storage

The following general best practices apply to all types of biospecimens, such as wet tissue, frozen tissue, paraffin-embedded tissue, glass slides, blood, serum, and urine. Individual types of biospecimens should be handled according to SOPs specific to the biospecimen type and the biomolecules to be analyzed—e.g., ribonucleic acid (RNA), deoxyribonucleic acid (DNA), protein, and lipid—when possible, recognizing that collection in the context of a clinical trial might be constrained by trial-specific protocols. Although most of the practices in this section assume freezing or formalin fixation of samples, dry or ambient temperature storage procedures may be appropriate for many samples [38, 46].

B.2.6.1.

Standardized protocols should be applied consistently in storing biospecimens to ensure quality and to avoid introducing variables into research studies. Biospecimen resource personnel should record storage conditions along with any deviations from SOPs, including information about temperature, thaw/refreeze episodes, and equipment failures [15]. Validation of storage equipment, for example, identifying “hot spots” in a freezer and ensuring that back-up equipment and temperature monitoring systems are functional, is essential.

B.2.6.2.

Biospecimens should be stored in a stabilized state. As discussed in previous sections, unnecessary thawing and refreezing of frozen biospecimens or frozen samples of biomolecules extracted from the biospecimens should be avoided, and appropriate size for aliquots and samples should be determined in advance to avoid thawing and refreezing of biospecimens. When thawing/refreezing is necessary, a biospecimen resource should follow consistent and validated protocols to ensure continued stability of the analytes of interest. Methods such as inventory tracking should be established to minimize disruption of the stable environment during sample retrieval; this is a requirement for accrediting agencies ([43, 47] [BAP.02900](#)).

In selecting biospecimen storage temperature, consideration should be given to the biospecimen type, the anticipated length of storage, the biomolecules of interest, and whether study goals include preserving viable cells [15, 48]; these are required by accrediting agencies ([43] [BAP.04200, 04300](#)). Paraffin blocks should be stored at temperatures below 80 °F (27 °C) in an area with pest and humidity control. Blocks stored in areas above these ‘room temperatures,’ duration of fixation, and most importantly humidity fluctuations have been shown to seriously compromise the expression of certain antigens when evaluated by immunohistochemistry [49].

In the case of liquid biospecimens, such as blood, consideration should be given to produce components such as plasma or serum, which should be separated before storage to preserve each constituent under its optimal condition. Whole blood (rather than fractionated blood) cryopreservation may be an efficient and cost-effective option for processing viable cells in large-scale studies [48, 50]. When in doubt as to possible future uses, tissues should be stored in the vapor phase of liquid nitrogen freezers or frozen at -80 °C to ensure long-term viability. Lower storage temperatures and cryoprotectant (such as dimethyl sulfoxide) may be used to maintain viable cells for long periods of time [15]. The difference in temperature between the bottom and top of a liquid nitrogen freezer should be measured and taken into consideration in planned analyses; the temperature at the top of a liquid nitrogen freezer is consistently below -140 °C. Regular temperature mapping of the interior of freezers is recommended to insure uniform temperature through the storage unit, and is required by accrediting agencies ([43] [BAP.08100](#)).

B.2.6.3.

Storage vessels should be stable under planned storage conditions [15, 51]. Biospecimen containers should be chosen with analytical goals in mind and evaluated prior to use to ensure that contamination or chemical leaching into the biospecimen does not occur. Vial size and number should be suitable for typical aliquots and anticipated investigator uses. Optimal volume and type of containers may prevent sample loss and minimize the costs of collection, storage, and retrieval. Screw-cap cryovials may be used for long-term, low-temperature storage; glass vials or vials with popup tops are unsuitable for long-term storage [15]. Snap-frozen biospecimens should be wrapped in aluminum foil or placed in commercial storage containers to minimize desiccation [51]. Labeling and printing systems should be chosen for stability under the long-term storage conditions appropriate for the biospecimen. Face shields and appropriate gloves should be worn for worker protection (see [Section B.4](#), Biosafety).

For optimal preservation, formalin-fixed, paraffin-embedded tissue should be stored as a block and not sliced until analysis is imminent because degradation will occur under even the best storage conditions (for

a review see [52]). However, when slide-mounted cut sections must be stored prior to analysis several steps may be taken to minimize degradation, including thorough dehydration and processing prior to storage, and storing the slides frozen and protected from exposure to moisture [52]. Optimal storage conditions might vary according to the final use to which stored sections will be put ([52], and empirically determining the optimal storage conditions is recommended.

B.2.6.4.

Each biospecimen should have a unique identifier or combination of identifiers that are firmly affixed to the container, clearly and legibly marked, and able to endure storage conditions. All other relevant information should be tied to this identifier, bearing in mind research participant confidentiality, security, and informed consent provisions. Inventory systems should relate the presence of each aliquot to its position in a specific box, freezer, refrigerator, or shelf. Consideration should be given to the location of biospecimens within storage containers to allow for the most efficient strategies for subsequent retrieval; i.e., by study and by material type within studies, as appropriate. Additional information related to biospecimen resource informatics best practices can be found in [Section B.6](#), Biospecimen Resource Informatics. A well-defined tracking system is a requirement by accrediting agencies ([43] [BAP.02800, 02900](#)).

B.2.6.5.

Automated security alarm systems should be in place to continuously monitor the function of storage equipment and should have the capability to warn resource personnel when equipment failure has occurred. Backup equipment, such as an alternative power source, should be set to activate automatically when necessary and should be tested regularly. Alternate cooling sources also might be needed in some cases. Written SOPs that are tested on a routine basis should be in place to respond to freezer failures, weather emergencies, and other disaster recovery/emergency situations ([15, 43] [BAP.09200, 09300, 09400](#)).

B.2.6.6.

Specimens should be stored in a secure location with limited access only by authorized personnel.

B.2.7. Biospecimen Retrieval

Samples should be retrieved from storage according to biospecimen resource SOPs that safeguard sample quality.

B.2.8. Shipping Samples

B.2.8.1. Shipping Conditions

B.2.8.1.1. When seeking to regulate sample temperature during shipping, the shipping time, distance, climate, season, method of transportation, and regulations as well as the type of samples and their intended use should be considered [15, 53]. To maintain proper temperature during shipping, appropriate insulation, gel packs, dry ice, or liquid nitrogen (dry shipper) should be used and these materials should be qualified for their intended use. To maintain refrigerated temperatures (2° C to 8° C), gel packs conditioned at -15° C or phase-change material rated for refrigerated transport may be used. To maintain frozen temperatures, gel packs conditioned at or below -20° C should be used. For frozen temperatures at -70° C, dry ice pellets or sheets should be used; dry ice is considered a hazardous substance for shipping purposes. For maintaining temperatures at or below -150° C, a liquid nitrogen dry shipper should be used [15]. Insulated packaging may be used to protect biospecimens from extremely hot or cold ambient conditions. Whenever intending to maintain samples below ambient temperature, enough refrigerant should be included to allow for at least a 24-hour delay in transport[15]. Temperature-sensitive material should be handled by a courier with resources to replenish the refrigerant in case of a shipping delay [15]. A simple colorimetric or other constant temperature-measuring device should be included with biospecimen shipments to indicate the minimum and/or maximum temperature within the shipping container.

B.2.8.1.2. Paraffin blocks and slides may be shipped at room temperature in an insulated package via overnight carrier. The use of insulated packages is considered important to minimize the effect of temperature fluctuations and to protect the blocks from temperatures higher than 27° C. There is convincing research that tissues stored in FFPE blocks may rapidly lose antigen expression for certain immunomarkers even when maintained in hospital storage areas at ‘room temperature’, which may fluctuate widely in non-temperature controlled areas [49]. Flat biospecimens, such as dried blood samples on absorbent pads or cards, may be enclosed in watertight plastic bags and shipped in a sturdy outer package or commercial envelope. Samples on glass or plastic slides should be cushioned and shipped inside a sturdy (not flexible) outer package. Inclusion of a simple maximum temperature indicator in each package and documentation of the maximum temperature upon receipt are recommended.

B.2.8.1.3. The number of biospecimens per package also affects whether the appropriate temperature can be maintained for all biospecimens in the shipment. A test shipment (e.g., frozen water samples) should be made before shipping extremely valuable samples to check the adequacy of coolants and any potential obstacles to a successful shipment. In addition, conditions throughout a critical shipment should be monitored by enclosing a device that records temperature during transport.

B.2.8.2. Shipping Documentation

B.2.8.2.1. Upon planned shipment of a package, documentation of the transfer in the form of a material transfer agreement (MTA) and requisition from the resource inventory is needed. An [MTA or similar agreement](#) ([Appendix 4](#)) governs the transfer of research materials and any associated data between two organizations. The MTA governs the rights and obligations of the provider and recipient with respect to the materials, and it should be consistent with all applicable laws, regulations, policies, and terms for transfer of those particular materials. The MTA also governs any timelines, commercialization, or third-party transfer of the materials and data ([15], Section M2.600).

B.2.8.2.2. Biospecimens should be shipped from an attended shipping facility or picked up for shipping by an appropriately authorized person. The biospecimen resource should notify the recipient before shipping to confirm that someone will be present to accept the package and properly store the samples. Shipments from and to the biospecimen resource should be tracked in a written or computerized shipping log [15], which should include shipment/invoice number, recipient (or source), date shipped (or received), courier name and package tracking number, sample description, number of samples shipped (or received), condition on arrival, study name and number (if available), key investigator’s name, and signature of biospecimen recipient [15].

Standardized paperwork should accompany shipments. Biospecimen resource personnel should electronically send a shipping manifest, a list of sample identification numbers, and descriptions of samples to the biospecimen recipient and should include a hard copy of the manifest inside the shipment. Identifying data should be available for the use of shipping or customs agents as well; some shipping agents require an itemized list of contents between the inner and outer packaging of diagnostic biospecimens.

Upon receipt, biospecimen resource personnel should verify biospecimen labels and any other documents or data shipped with the biospecimens against the packing list for consistency and correctness. A questionnaire requesting feedback about the quality of samples received may be enclosed in each shipment for quality management purposes [15].

In general the concept and procedures for *chain of custody* should be applied when shipping biospecimens ([15], Section G, Records Management).

B.2.8.3. Regulatory Considerations

B.2.8.3.1. All applicable laws and regulations for shipment should be satisfied. For example, ISBER Best Practices and International Air Transport Association (IATA) regulations [15, 53] should be consulted for information concerning international transport regulations and classifying samples for shipment. Variation in national and regional standards regarding biospecimen transport should be considered when shipping biospecimens to or from an international location.

B.2.8.3.2. Additionally, Occupational Safety and Health Administration (OSHA) regulations on toxic and hazardous substances [54] (29 CFR 1910 Subpart Z) should be consulted to determine whether a substance requires a biohazard label. Additional safety considerations are enumerated in [Section B.4](#), Biosafety.

B.2.8.4. Training

Biospecimen resource personnel should be trained to ship samples appropriately. Periodic retraining according to governing regulations should be conducted and documented [15].

B.3. Quality Management

B.3.1. Quality Management System

Biospecimen collection, processing, management, and distribution should be carried out within a quality management system (QMS) that contains documented quality assurance/quality control (QA/QC) policies and written SOPs. Where feasible, the QMS should be managed by individuals who are not involved in repository operations, although this might not be possible for smaller or less established biospecimen resources. The QMS describes the biospecimen resource's QA/QC policies and approaches for ensuring that program requirements are met. Each biospecimen resource should either establish a written QMS or adhere to a QMS published by the organization with which the biospecimen resource is associated. There are several common quality management programs available upon which to pattern individual biospecimen resource QMS policies. No particular approach is recommended, but several are mentioned below to help design the appropriate QMS for the biospecimen resource. When a resource is considering a quality management program, and choosing between GLP, CLIA and ISO, there are many considerations such as if the resource has legal obligations to state and federal laws, type of resource, cost, and many other variables. One size quality program does not fit all.

The following Web sites are relevant to the development of a QMS:

- ISBER
<http://www.isber.org>
- Good Laboratory Practices <http://www.oecd.org/chemicalsafety/testing/goodlaboratorypracticeglp.htm>
- Clinical Laboratory Improvement Amendment
<http://wwwn.cdc.gov/clia/>
- International Organization for Standardization (ISO9001:2008, 2015)
<http://www.iso.org>
- U.S. Food and Drug Administration (FDA) Quality System Regulation, 21 CFR 820
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=820>

B.3.2. Quality Assurance/Quality Control

Formalized QA/QC policies should be developed by biospecimen resources to minimize circumstances that could adversely affect scientific results; to ensure the safety of personnel; to aid in the efficient operation of the resource; and to increase the confidence of users that the quality, quantity, and annotations of the biospecimens are as purported. QA/QC policies should be customized for the intended and potential uses of the biospecimens in a given biospecimen resource. QA/QC implementation should ensure that accurate data accompany

biospecimens that are to be analyzed for diagnostic as well as research purposes. The following are key issues for QA/QC implementation and auditing:

- Staff proficiency
 - Staff organization and responsibilities.
 - Training and competency programs for personnel as appropriate; e.g., training in human subjects protections and privacy regulations such as the Health Insurance Portability and Accountability Act (HIPAA) training, safety training, or bloodborne pathogen training.
 - Competency assessment as documentation of training.
 - Documentation of staff compliance with policies and procedures.
 - Risk mitigation, disaster response, and emergency preparedness.
- Facility infrastructure
 - Equipment validation and change control, calibration, maintenance, repair procedures, and environmental monitoring; e.g., temperature monitoring of freezers.
 - Supplier management program, including inspection and validation of reagents and other supplies.
- Biospecimen control and documentation
 - Control of biospecimen collection, processing, and tracking.
 - Documentation of biospecimen collection, processing, and tracking, with detailed annotation of pre-analytical parameters (see [Section B.6](#), Biospecimen Resource Informatics).
 - Measurement and analysis of key process indicators to drive quality improvement.
 - System security.
- Recordkeeping and document control
 - Employment of a data quality management, assessment, and reporting system.
 - Clinical data records.
 - Accessibility of policies and procedures.
 - Documentation records, including audit reports, deviation reports, and corrective action/preventive action reports.
 - External document monitoring to ensure that the facility remains up to date with relevant laws, standards, and best practice publications.
 - Staff training records, including record of staff adherence to training schedules.
 - Data quality management (source documentation and electronic records), assessment of reporting system.
 - Supply records.
- Internal audit of program and its policies, scheduled and unscheduled
 - Audit for accuracy of all annotation data; e.g., the biospecimen is where it is purported to be, in the purported volume, with the appropriate labels/identifiers.
 - Audit for accuracy of patient data associated with biospecimens; e.g., age, gender, diagnosis, etc.
 - Audit of compliance of biospecimen resource with institution policies; e.g., human subjects and privacy and confidentiality protections, prioritization of biospecimen use, etc.
 - Audit of SOPs for all activities and processes.
 - Each biospecimen resource ensures that SOPs are written, reviewed, and appropriately approved.
 - Process exists for review and updating at designated time intervals.

B.3.3. Standard Operating Procedures Manual

Each biospecimen resource should develop SOPs that state policies and describe relevant processes in detail. Additionally, a document control program and policies for governing, modifying, or revising SOPs should be at each biospecimen resource. All SOPs should be reviewed on a periodic basis or whenever significant changes in practices, procedures, technology, law, or regulation necessitate an update. The SOPs should be well structured and undergo a rigorous approval process. Upon implementation, all SOPs should be followed as written. Current copies of SOPs (SOPs manual) should be stored in designated locations and available to personnel at all times. Personnel should review new and revised SOPs prior to implementation; reviews and associated trainings should be recorded. Generally, especially for larger biospecimen resources which have the personnel to support a more comprehensive QMS, an electronic document control system should be implemented. One example is MasterControl™, which is described on their web site [55]:

“The MasterControl™ GxP process management suite consists of configurable, easy-to-use, and connected applications for automating, streamlining, and effectively managing GxP processes throughout the entire product development process from conception to commercialization. Hundreds of companies worldwide rely on MasterControl to facilitate compliance with FDA, and other worldwide regulatory bodies (e.g., GxPs, 21 CFR Parts 11, 210-211, 820, 606), and ISO quality standards (e.g., ISO 9000, ISO 13485, ISO 14000, ISO/TS16949) to improve product quality and safety - and to ensure compliance.”

Note that the mention of any particular product such as MasterControl does not comprise an endorsement by the NCI.

B.3.3.1. Contents

Specifically, the SOPs manual and/or electronic document control system as described above should minimally include the following information:

- *Informed Consent.* Each biospecimen resource should have documentation of the informed consent status for each biospecimen. In addition, procedures for obtaining informed consent and protecting the privacy of identifiable human research participants and confidentiality of data should be clearly described, as should procedures to follow in the case of withdrawal of consent.
- *Equipment Monitoring, Calibration, Maintenance, and Repair.* Each biospecimen resource should have procedures to routinely monitor devices that are used for biospecimen storage or preparation. This includes ensuring that equipment is accurately calibrated, that operational settings are routinely recorded, and that scheduled maintenance and repairs are documented. Equipment SOPs and records should also cover associated backup and emergency notification systems.
- *Control of Biospecimen Collection Supplies (Disposables and Reagents).* Each biospecimen resource should have procedures to ensure that consumable supplies and reagents used for collection, processing, and storage conform to required standards. This includes ensuring purchased supplies are approved, are acquired from approved vendors, meet defined material specifications, and are in good condition for use.
- *Biospecimen Identification and Labeling Conventions.* Each biospecimen resource should define policies and procedures for labeling (coding) biospecimens and linking biospecimens to other data sets and patient informed consent.
- *Biospecimen Collection and Processing Methods.* Each biospecimen resource should define, in sufficient detail to allow replication, the procedures associated with biospecimen collection, handling, processing, and preservation for each biospecimen type. This includes detailed descriptions of supplies, equipment, methods, and processing for division of a biospecimen into multiple aliquots. Biospecimen collection and processing should always include the recording of personnel names, dates, and times to accurately record these potential sources of pre-analytic variation.

- *Storage and Retrieval.* Each biospecimen resource should define procedures for the storage and retrieval of biospecimens from a biorepository, including processes for adding new biospecimens, withdrawing biospecimens, responding to and filling requests, and final disposition of biospecimens.
- *Shipping and Receiving.* Each biospecimen resource should have defined procedures and policies for the packaging and transport of ambient temperature and frozen biospecimens to ensure biospecimen integrity and safety. This includes packaging specifications to maintain appropriate temperature conditions; wet ice, dry ice, and liquid nitrogen handling; shipment temperature monitoring; shipment regulations for hazardous materials; shipment logs; delivery notifications; confirmation of delivery; shipment feedback mechanisms; and MTAs or other appropriate agreements to cover transfers (see [Section B.2.8](#), Shipping Samples).
- *Laboratory Tests Performed In-House Including Biospecimen Quality Control Testing.* Each biospecimen resource should have SOPs governing standardized in-house testing procedures and should document the results in associated quality records. This includes tests to assess and control biospecimen quality, such as confirmation of histopathology diagnosis, nucleic acid integrity, or biomarker expression.
- *Biospecimen Data Collection and Management (Informatics).* Each biospecimen resource should have policies for managing records and procedures defining data access, data collection methods, reporting, data QC, and standardized medical terminology (see [Standardized Systems for Clinical and Pathology Data](#), and [Section B.6](#), Biospecimen Resource Informatics).
- *Biosafety.* Each biospecimen resource should have policies and procedures covering biosafety, including reporting staff injuries, as well as standard precautions for bloodborne pathogens, personal protection equipment, hazardous material handling, and disposal of medical waste and other biohazardous materials (see [Section B.4](#), Biosafety).
- *Training.* Each biospecimen resource should have policies and procedures for training of all staff members. Such training should be documented and include policies and procedures to manage corrective actions; to resolve inventory and shipment discrepancies; to monitor all sample storage; and to manage power outages, emergencies, and natural disasters.
- *Security.* Each biospecimen resource should have procedures for administrative, technical, and physical security, including procedures for information systems security [\[56\]](#). Security SOPs and policies should include information on points of contact and designated backup personnel, including names and emergency contact numbers.

B.3.3.2. Implementation

The biospecimen resource director and/or the individual responsible for the QA/QC program should review and approve all SOPs and associated process validation studies prior to implementation. Upon implementation, all SOPs should be followed as written, and any deviations from written SOPs should be clearly noted. Effectiveness of QA/QC measures should be evaluated on a routine basis.

B.4. Biosafety

Laboratories and biospecimen resources that handle biospecimens expose their employees to risks involving infectious agents and chemicals as well as the general dangers of a laboratory. A predictable yet small percentage of biospecimens will pose a risk to biospecimen resource personnel who process them. Consequently, all biospecimens should be treated as biohazards [\[57\]](#). In addition to taking biosafety precautions, biospecimen resources should adhere to key principles of general laboratory safety. See ISBER Best Practices [\[15\]](#) Appendix A for additional internet references concerning laboratory and biobank biosafety. Also see the NIH Office of Science Policy's Biosafety Guidance web site [\[58\]](#)

B.4.1. Biohazard Precautions

B.4.1.1.

Laboratories and biospecimen resources should assume that all human specimens are potentially infective and biohazardous [57]. For example, OSHA regulations [54] (29 CFR § 1910.1030(f)(1)(i)), as applicable, require that employers “make available the hepatitis B vaccine and vaccination series to all employees who have occupational exposure, and post-exposure evaluation and follow-up to all employees who have had an exposure incident.” Dried blood, tissue, urine, saliva, cerebrospinal fluid, dura mater brain tissue and other biospecimens should be handled according to standard precautions and labeled according to applicable OSHA requirements. Biospecimen resource work practices should be based on standard precautions similar to those used in laboratories and clinical settings. Two basic safety precautions should be followed in laboratories and biospecimen resources that handle biospecimens: (1) Wash hands frequently, and (2) always wear face protection and gloves when handling biospecimens or working within or around freezers [59]. Additional good general laboratory work practices are outlined by Grizzle and Fredenburgh and in the NIH biosafety guidelines [57, 58].

B.4.1.2.

A biospecimen resource should establish clear policies regarding the inclusion or exclusion of biospecimens with varying levels of risk. For example, depending on the potential for exposure by splash or aerosol, human specimens of unknown infectivity should be handled according to biosafety level-2 (BSL-2) conditions, as outlined in the Centers for Disease Control and Prevention (CDC)/National Institutes of Health (NIH) booklet “Biosafety in Microbiological and Biomedical Laboratories” (BMBL) [59]. At BSL-2, when biospecimen containers are opened for processing, they should be handled in a BSL-2 biological safety cabinet (hood). All biospecimen resources that handle human specimens should operate under the applicable OSHA bloodborne pathogens standard and develop an exposure control plan [54] (29 CFR § 1910.1030). Additional precautions should be applied, as outlined in the BMBL. Some activities, such as droplet-based sorting procedures [60], may require higher containment, but in other cases, less stringent practices may be acceptable. Therefore, biospecimen resource staff members should be trained to perform risk assessments and determine appropriate levels of containment.

B.4.1.3.

Biospecimen resources should establish policies consistent with the CDC’s “Select Agents and Toxins” regulation [61] (42 CFR Part 73), as applicable. This regulation implements provisions of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, setting forth the requirements for possession, use, and transfer of select agents and toxins. The biological agents and toxins listed as Select Agents and Toxins (e.g., botulinum neurotoxins, Ebola virus) have the potential to pose a severe threat to public health and safety, to animal health, and to animal products.

B.4.2. Biosafety Best Practices

B.4.2.1.

Biospecimen resources should be familiar with governmental and accrediting agency requirements regarding biohazards and sources of current information concerning laboratory biosafety for use in developing an overall program in safety and associated training programs (see CDC/NIH documents referenced in [Section B.4.1](#), Biohazard Precautions).

B.4.2.2.

Biospecimen resources should identify risks and other general issues of biosafety. Frequent biospecimen resource activities should be identified, safety issues involved with each activity analyzed, and suitable controls implemented.

B.4.2.3.

Written working guidelines that are based on Federal and State requirements, experience, and published information should be developed to improve biosafety. These guidelines should be reviewed and updated regularly and modified in response to problems or if they prove ineffective.

B.4.2.4.

A training program should be developed and implemented. Each employee should receive training in relevant areas of biosafety before beginning work, and the training should be updated annually. Training for biorepository personnel should include any site- and/or building-specific emergency procedures.

B.4.2.5.

Biospecimen resources should record and arrange for treatment in response to all incidents where personnel are exposed to biohazards or are potentially infected.

B.4.3. General Laboratory Safety

In addition to biosafety, biospecimen resources should follow strict general safety regulations and procedures regarding chemical, electrical, fire, physical, and radiological safety (ISBER 2012 Best Practices [15], Appendix A; OSHA General Industry Standards [62] 29 CFR 1910).

B.5. Collecting and Managing Clinical Data

Appropriate annotation of biospecimens is crucial to the overall usefulness of the biospecimen resource for scientific research [63].

Biospecimen resources store collected biospecimens using multiple methodologies and procedures. Researchers rely on banked biospecimens for a wide variety of purposes, using different platforms and technologies. The data recorded by investigators and biospecimen resources depend on the types of biospecimens collected and the studies' objectives.

B.5.1. Regulatory Compliance

Data collection activities should conform to U.S. Food and Drug Administration (FDA) requirements [64] (21 CFR Part 11), if and where applicable, so that the data may be cited and/or used in Investigational New Drug and Investigational Device Exemption applications.

B.5.2. Collecting Clinical Data**B.5.2.1. Privacy regulations**

As appropriate for the purpose and nature of the biospecimen resource, relevant clinical data associated with a biospecimen should be collected in accordance with applicable privacy statutes and regulations, and human subject protection regulations governing the acquisition of biospecimens and associated clinical data (see [Sections C.2](#), Informed Consent, and [C.3](#), Privacy and Confidentiality Protections, for additional information and references). Clinical data associated with the biospecimens should be used and disclosed only for research and development in compliance, as applicable, with HIPAA and HITECH, with U.S. Department of Health and Human Services (HHS) and FDA human subject protection regulations, and with applicable State and local laws.

B.5.2.2 Collection requirement updates.

Biospecimen resources should track researchers' requests for biospecimens with specific clinical data to guide the refinement of clinical data collection, as appropriate, based on the intended purpose of the resource, and if the biospecimen resource is the point of access for biospecimens and associated clinical

data. Biospecimen resources should routinely summarize this information and provide it to an entity that maintains and/or collects the clinical data in order to improve the collection of clinical data.

B.5.3. Longitudinal Clinical Data

B.5.3.1 Data types

If the study design and objectives require, biospecimen resources should collect and store longitudinal data following applicable informed consent and authorization requirements. Based on these requirements, information linked to biospecimens may include demographic data, lifestyle factors, environmental and occupational exposures, cancer history, structured pathology data, additional diagnostic studies, information on initial staging procedure, treatment data, and any other data relevant to tracking a research participant's clinical outcome (see examples in the Minimal Clinical Data Set, [Appendix 1](#) for a recommended set of Common Data Elements (CDEs) that may be included). Different biospecimen resources may require more or less detailed annotation based on the primary intended use of the biospecimens. The dataset for clinical annotation should be based on the needs of the biospecimen resource users, as well as overall feasibility, particularly for biospecimens collected from clinical trials.

B.5.3.2. Database and data access

Databases developed for longitudinal studies should use coded data associated with a biospecimen but should maintain a secure link to identify the research participant to allow additional longitudinal data to be obtained, if permitted by law and by the research participant's consent/authorization. Policies and protocols should be in place to facilitate access to uniform longitudinal data (e.g., treatment and outcome information, as appropriate) while protecting research participant's privacy and confidentiality.

B.5.3.3.QA/QC

To collect high-quality longitudinal information, biospecimen resources should ensure that dedicated and trained personnel curate longitudinal clinical data with validation of the collection process and QA/QC.

B.6. Biospecimen Resource Informatics: Data Management and Inventory Control and Tracking

Driven by the scale of data generated by the cutting-edge –omics technologies, informatics systems have become critical to the research enterprise. A minimum set of functional, operational, and legal requirements should be considered best practices (as outlined in this document) and should be incorporated when developing or selecting informatics systems to support biospecimen resources.

B.6.1. Functionality—General

B.6.1.1. Data types

At the biospecimen resource level, informatics systems should be focused on recording data types as described in Section B.5. This includes inventory functions, tracking all phases of biospecimen acquisition, processing, handling, QA/QC, biospecimen quality measurements (such as RNA Integrity Numbers), and distribution from the collection site (research participant) to utilization (researcher).

B.6.1.2. Identifiers

Each biospecimen should have a unique ID assigned to it in the system. The informatics system should have the capability of linking the labels on the physical biospecimen container (e.g., paper labels or barcodes) to other information regarding that biospecimen in the system.

B.6.1.3. Association of biospecimen data with clinical data

Informatics systems should track clinical data associated with a biospecimen and/or link biospecimen data with external sources of clinical data, where applicable.

B.6.1.4. Security

Biospecimen resource informatics systems should provide role- and project- based access control to system functionality and data. The role-based access control (RBAC) should support at least the flat National Institute of Standards and Technology (NIST) level, and preferably the hierarchical level as well [65]. Project based security should implement a separate RBAC for access to data based on project/study/protocol privileges.

Biospecimen resource informatics systems that store protected health information (PHI)/ personally identifiable information (PII) should adhere to all security regulations for such data (e.g. HIPAA, HITECH). These systems should also meet the criteria for NIST data stored and accessed at the FISMA moderate level [66].

B.6.1.5. Data Access Logs

Biospecimen resource informatics systems should provide vital system statistics and audit logs of all access to PII/PHI in the database.

B.6.2. Functionality—Identification and Tracking of Biospecimens**B.6.2.1. Standard Definitions**

For informatics purposes, a biospecimen refers to a physically distinct specimen usually stored in a single container. Multiple physical parts created by extraction, division into aliquots, or other physical division of a biospecimen are considered new biospecimens and are referred to in this document as samples, sometimes referred to elsewhere as derived (or child) samples, each requiring a new identifier. The origin of each sample should be recorded. Biospecimen resources should define standard terms for all lineages of biospecimens, from initial collection to subsequent divisions and extractions. Biospecimen resources should employ an existing standard terminology or modify an existing standard to harmonize data elements for semantic interoperability.

B.6.2.2. Unique Identifiers and Labels

There is a functional need to employ a method to assign either a global unique identifier (GUID) or a method to maintain the integrity of the original identifier for each biospecimen. There are research needs to verify and trace back to the original source biospecimen when its associated aliquots/derivatives are used. In addition, as biospecimens and derived samples are shared among biospecimen resources, QC questions rely on having a global unique identifier to ease traceability (see [Section B.2.6.4](#)).

Each biospecimen should be assigned a unique identifier or combination of identifiers, such as a number and/or barcode, which should not be reflective of its identity (i.e. current storage location position, clinical data, patient identifiers, etc). This recommendation is most applicable to future biospecimen collections because implementation in existing collections would be laborious. In this context, the scope within which identifiers are unique applies to an individual system and the biospecimen resources it supports, although it is recommended that if a global identifier is able to be assigned, it should be used wherever possible.

For all biospecimens, labels should be printed in both machine-readable and human readable formats. The label should link back to the inventory management software.

B.6.2.3. Tracking Significant Events

The informatics system should be able to track a biospecimen through significant events from collection through freezing/thawing, processing, storage, distribution, and possible destruction. This includes tracking of amount distributed and amount remaining of partially-used biospecimens. Restocking of returned, unused samples from the researcher—while not recommended because of potential effects of unknown handling on sample quality—should also be tracked. Tracking includes cross-referencing multiple, pre-existing, and/or external physical biospecimen identifiers, such as barcodes with non-identifying information. Any data about the sample being compromised should be noted and available to the user.

B.6.2.4. Position Identification and Updates to Location

The biospecimen resource database should be updated each time a biospecimen or sample is moved within or out of the biospecimen resource, and the informatics system should be able to track the location changes of the sample. The database must be able to identify each position in storage (i.e. the positions in the box, the box, rack, and freezer). Different storage configurations should be supported (i.e. upright and chest freezers, LN2 tanks, straws).

B.6.2.5. Query Capability

The biospecimen resource database should provide full query capability throughout the system.

B.6.2.6. Audit Trail

The biospecimen resource database should provide audit trail capability in order to track all changes made to the data, including but not limited to all specimen data, system metadata, and clinical data. The computer-generated and automatic reports should include: original data and new data; date and time changed; how the change was made; who made the changes; why the changes were made.

B.6.2.7. Annotation

Since a repository may track samples of many different studies or from different collections, consideration should be given to what the inventory management database can contain and what should be stored in an external database and linked to the inventory via a unique identification number (UID). In the case of human specimens, consideration should be given to storing confidential patient clinical information separately from inventory data such as sample information and location.

The informatics system may also be designed to handle digitally-scanned documents related to the sample. Relevant documents may include pathology reports, clinical lab reports, donor consent forms, material transfer agreements or necessary permit documentation.

B.6.3. Interoperability

B.6.3.1. General

Although biospecimen resources may have different informatics requirements based on workflow that require different informatics systems, these systems should be interoperable to integrate clinical and research data and establish distributed biospecimen resources. This interoperability should enable integration with local systems and authorized external systems.

B.6.3.2. Standards

The informatics systems should utilize data elements from a common metadata repository. Even if the systems utilized non-standard data elements for storage internally, the system design should allow for configurable translations to one or more established standards.

B.6.3.3. Regulation

Integration with clinical data systems should conform to HIPAA, HITECH, and other regulations and laws as applicable to the systems purpose, scope, and jurisdiction.

B.6.3.4. Interface

Data systems should provide a published application programming interface (API) for other systems to interact with. Changes to this interface should remain backwards compatible as much as possible in order to minimize disruption for connecting systems. The API implementation should include both automated conformance and interoperability testing to ensure robustness.

B.6.3.5. Security

Interoperability APIs should support a security layer at least as secure as other system interfaces. The API should enforce all business and security rules on connecting systems. Evaluation of the systems API should be measured against National Institute of Standards and Technology (NIST) guidelines, i.e. the NIST Special Publication 800-30, Guide for Conducting Risk Assessments [56].

B.6.3.6. Data Sharing

Biospecimen resource informatics management systems should be capable of sharing appropriate, de-identified biospecimen data to users at remote locations for multiple purposes including satisfying reporting and regulatory requirements as well as searching for potential biospecimens for a proposed scientific study. The NIH has developed the NCI Specimen Resource Locator [67], a tool for interoperability that aids biospecimen resources in distributing and locating biospecimens.

B.6.3.7. Results Data

If the results data is stored in the biobank information management system, then it must adhere to all of the criteria listed above.

B.6.4. Selection of Biospecimen Resource Informatics Management Systems**B.6.4.1. Organizational Requirements**

Biospecimen resources should engage all stakeholders (IT office, clinicians, researchers, etc.) in the requirements gathering phase to identify system features and functionality. The organizational requirements for a tracking system should reflect the needs of all users and should comply with data protection policy. Use case scenarios are a recommended tool to document the needs of all users.

B.6.4.2. Technical Requirements

Biospecimen resources should identify the minimum set of requirements such as:

- Computing platforms
- Scalability requirements
- Performance requirements
- Connectivity requirements

Common requirements to gather and evaluate are: biospecimen tracking, biospecimen processing and history, data entry, data verification, querying and reporting, label printing/scanning, audit trails,

interoperability, security, scalability, validation and implementation requirements, infrastructure requirements, IT support requirements, number of users, cost for purchase and maintenance.

B.6.4.3 Information Management Systems Evaluations

Biospecimen resources should use criteria identified above to judge mature and commercially available systems, taking into account the specific organizational and technical requirements. It is critical that the original stakeholders are involved at all phases of the evaluation process.

As part of the evaluations, an assessment of the system provider must be performed for their capability to provide implementation, support, and ongoing maintenance.

B. 6.4.4 Build versus Buy System

This is a complex question with many considerations on resources, personnel, schedules, budgets, politics, and organizational bias. Building a customized system will allow the biospecimen resources to have the interface to exactly meet the operational requirements and workflow, but requires resources, funding, and a commitment to ongoing maintenance. Purchasing a system allows the biospecimen resources to take advantage of existing technology at a reduced cost and implementation timeline, but with an interface that does not precisely map to the original needs. There is no standard answer to this question; individual biospecimen resources must review the system requirements and make a strategic decision on the best path forward for the organization.

B.6.5. Validation and Operation of Biospecimen Resource Informatics Systems

B.6.5.1. Dependability

Biospecimen resource informatics management systems should have an operational infrastructure to support operation access 24 hours a day, 7 days a week.

B.6.5.2. Disaster Recovery

Biospecimen resource informatics management systems should have processes defined and in place to cope with system downtimes and disaster recovery. System backups and restores should be tested on a regular basis to ensure the quality of the backup media and the restore process. All data stored outside the system should be encrypted to secure PHI/PII.

B.6.5.3. Quality Control

Biospecimen resource informatics management systems should be periodically evaluated to ensure that the system is fulfilling the criteria advised in best practices and the latest needs of the biospecimen resource. Random quality control checks should be performed on the physical inventory confirming that the physical location of stored biospecimens matches that provided in the informatics system. All system tools and methods should be validated to ensure their accuracy in performing that task.

B.6.5.4. Physical Security

All biospecimen resource databases at an individual institution should be in a secure site monitored by the institution. Resources without the capabilities to provide such infrastructure should seek external hosting arrangements for their informatics system.

B.6.5.5 Software System Validation

Initial validation of the informatics system should be well-documented ensuring data integrity, accurate process workflow, and adequate audit trail. Regulations such as the FDA's 21 CFR Part 11 dictate requirements to include in the validation plan.

A detailed written validation plan must identify high risk areas in the software and how they will be thoroughly tested. Particularly susceptible areas are data migration points, data flow junctures, system configurable areas, and any customized features.

A new software implementation requires more comprehensive testing than an upgrade to an existing system. A system upgrade should include re-testing of updated program elements and any high risk areas of the program, whether presumed to be updated or not. To adequately test an upgraded system, a copy of the existing data should be used in a separate test environment.

Subsequent validation of each upgrade to the system should replicate a portion of the initial validation to prevent unidentified regression errors as well as a full validation of the upgraded portion of the system.

B.6.6. Regulatory Issues Pertaining to Informatics Systems

Besides those issues identified in the Ethical, Legal, and Policy section in these guidelines, the following regulatory issues should be addressed as applicable.

B.6.6.1. Regulations

Biospecimen resources should meet relevant regulatory requirements, including but not limited to:

- State and Federal Regulations
- Privacy Protection
- 508 Compliance
- Security Regulations

B.6.6.2. Security

Biospecimen resources should refer to the NIST Special Publication 800-30 Guide for Conducting Risk Assessments [\[56\]](#), as applicable, to determine the appropriate level of security for informatics systems.

B.6.6.3. HIPAA/HITECH

Any PHI or PII data stored in the informatics system should be flagged as such and masked from incidental viewing. Only those users with specific authorization to view this data should be allowed access. All access to this data should be logged in a secure, non-editable, permanent audit trail.

C. Ethical, Legal, and Policy Best Practices

In addition to technical issues relating to the physical integrity and quality of biospecimens, multiple ethical, legal, and policy issues should be considered in biospecimen research activities. Key ethical issues include respecting the autonomy of human research participants (human subjects²), protecting human research participants from breaches of privacy and confidentiality, and minimizing individual and group harms. Legal and policy issues include adhering to relevant Federal, State, and local laws and regulations surrounding the collection, storage, dissemination, and use of biospecimens; developing appropriate guidelines for biospecimen and associated data access; ensuring that biospecimens are used in scientifically meritorious research; and establishing biospecimen resource governance (Refer to [Sections C1](#) through [C6](#) for specific details about relevant regulations and policies).

In 2005, the NCI hosted a workshop that assembled diverse representatives from the cancer research community as well as ethics, legal, and policy experts to discuss and propose approaches that could help unify, integrate, and improve NCI-supported biospecimen resources and biospecimen research in general. The recommendations that resulted from this workshop as well as additional NCI-sponsored meetings and work conducted between 2002 and 2005 formed the basis of the *NCI Best Practices*, first published in 2007. The first revision to the *NCI Best Practices*, released in 2011, provided additional recommendations formulated during the 2007 NCI-hosted Symposium-Workshop on [Custodianship and Ownership Issues in Biospecimen Research](#). Featuring leaders from the academic community, private sector, patient advocacy groups, and Government agencies, this landmark symposium-workshop was convened to develop recommendations for best practices concerning the custodianship of biospecimens and associated data at NCI-supported resources and to expand upon the original *NCI Best Practices* in four key areas: (1) Considerations for human research participants, investigators, and institutions; (2) financial conflicts of COIs; (3) intellectual property (IP); and (4) access to products and benefits. Recommendations generated during this symposium-workshop comprise the 2011 revisions to Section C of the *NCI Best Practices*.

In this 2016 revision to the *NCI Best Practices*, the ethical, legal, and policy best practices have been updated based on more recent guidance concerning informed consent, return of research results and incidental findings, and community engagement. In addition, corrections and updates have been made to internet references for this growing area of research and policy.

Furthermore, investigators and biospecimen resources should consult their IRBs, as needed, and appropriate institutional officials to determine how Federal and State regulations and policies would apply to their resource and how to implement recommendations in the NCI Best Practices related to human subjects research as defined in 45 CFR Part 46. Biospecimen resources that expect to make samples available for NIH-funded research should be aware of NIH data sharing policies [\[68\]](#). In particular, if the samples will be used in an NIH-funded project generating large-scale genomic data [\[69\]](#), the NIH Genomic Data Sharing (GDS) Policy will apply and the genomic data and accompanying phenotypic data are expected to be submitted to an NIH-designated data repository. The GDS Policy has set forth expectations regarding informed consent [\[C.2\]](#), privacy and confidentiality [\[C.3\]](#), and access to data [\[C.3\]](#). Therefore, to maximize the utility of samples for NIH-funded research, biospecimen resources should anticipate that their sample collections will need to be consistent with NIH GDS Policy requirements. An NIH-funded project falls under the GDS Policy due to the type of data that it generated. The samples used in the project may come from a variety of sources, including biospecimen resources who are not otherwise actively involved in the project. For example, the investigators may have contacted a biobank known to have relevant samples, and obtained them through a standardized process. Another example is when the investigators reach out to a researcher who has been maintaining a sample collection in a lab, and asks them to be a collaborator and provide those samples through an MTA mechanism.

² The NCI views the terms “human research participant” and “human subject” as equivalent. The former term is used throughout this document in order to recognize the important and active role of patients and volunteers in research. “Human research participant” is intended to have the same meaning as human subject, as defined in [45 CFR Part 46](#).

As part of GDS Policy compliance, the project's principal investigator and institution must provide assurance for several steps in the research process. While this institution can assure that an IRB considered the risks of submission to an NIH-designated repository, and reviewed the investigator's plan for de-identifying the dataset consistent with the GDS, the institution may not feel comfortable attesting to aspects of the research process that occurred outside of the project and beyond the institution. These are typically the points in the institutional certification template that relate to the sample collection and informed consent:

- Any limitations on the research use of the data, as expressed in the informed consent documents, are delineated;
- An IRB, privacy board, and/or equivalent body, as applicable, has reviewed the investigator's proposal for data submission and assures that:
- The protocol for the collection of genomic and phenotypic data is consistent with 45CFR Part 46;
- Data submission and subsequent data sharing for research purposes are consistent with the informed consent of study participants from whom the data were obtained;

As such, biospecimen resources who have engaged with researchers whose projects fall under the GDS policy should be prepared to support the institutional certification process. It may be they will be asked to provide a statement/memorandum attesting to the points above, where appropriate. If the biospecimen resource is not able to attest to the points (e.g. when they did not collect the samples themselves), then the resource should be prepared to put the investigator in touch with the original sample source.

It will be most helpful to the institutional certification process if the biospecimen resource keeps records of the permitted future research use for the samples. Permitted future research uses should be included in any supporting documentation, as these will become the data use limitations used by an NIH Data Access Committee to determine which secondary researchers can access the data.

The ethical, legal, and policy best practices outlined in this document identify key regulations and recommendations relevant to biospecimen collection, storage, dissemination, and use in research. These best practices are more detailed and extensive than, for example, a grant policy statement; however, not every element outlined in the *NCI Best Practices* would apply to every biospecimen research activity. Investigators and biospecimen resource directors should consider these principles carefully in conjunction with the objective of the research project and the mission of the biospecimen resource to determine the most appropriate operational policies. Furthermore, investigators and biospecimen resources should consult their IRBs, as needed, and appropriate institutional officials to determine how Federal and State regulations and policies would apply to their resource and how to implement recommendations in the *NCI Best Practices* related to human subjects research, as defined in 45 CFR Part 46 [\[70\]](#).

The regulations and proposed standards discussed in this document are for research using biospecimens in the United States. Many countries have their own ethical, legal and policy standards for human subjects research including, in some cases, specific provisions for the use of biospecimens. Investigators and biospecimen resources should be aware of international standards that may be applicable and address any differences between international and U.S. regulatory requirements prior to the initiation of a new collaboration or collection.

C.1. Principles for Responsible Custodianship

Custodianship is the caretaking responsibility for biospecimens that extends from collection through research use. Responsible custodianship requires careful planning and transparent policies to ensure the long-term physical quality of the biospecimens and the integrity of associated data, the privacy of human research participants, the confidentiality of associated data, and the appropriate use of biospecimens and data. In the

interest of transparency, biospecimen resource policies should be made available to the public either electronically or for onsite inspection.

The custodian is the trusted intermediary and caretaker of biospecimens and associated data, and the custodian's caretaking responsibilities should align with applicable ethical and policy standards. The custodian should be clearly designated and, ideally, be someone other than the research investigator or sponsor(s) of the biospecimen resource; e.g., a biospecimen resource manager, to eliminate any potential conflicts of interest. When the research investigator is the primary holder of the biospecimens and data, he or she should have the same duties of custodianship and abide by the same ethics that apply to research use. Thus, principles concerning oversight and QC mechanisms that apply to traditional biospecimen resources could also be relevant to the collection, storage, distribution, and use of biospecimens in small collections held by individual investigators; e.g., [protection of the privacy of human research participants](#) and confidentiality of their data, well-documented [QA/QC procedures](#), etc. Alternatively, research investigators with small biospecimen collections that will be stored for future studies could consider joining an institutional IRB-approved biospecimen resource. This consolidation would help ensure baseline quality standards for smaller biospecimen collections.

In their role as trusted intermediaries, custodians and managers of biospecimen resources should establish a governance plan consisting of the set of authorities, processes, and procedures guiding key operational decisions made within the resource. Governance affects access to biospecimens as well as custodial relationships and responsibilities and should be part of the resource's general custodianship plan. In addition, biospecimen resources should demonstrate their accountability to promote public trust by accepting all of the custodial responsibilities listed below and, as appropriate, establishing advisory boards—with human research participants among the active members—to accomplish them.

- Implementing overall operational, ethical, and legal policies based on feedback from individuals and the community, where practicable and appropriate.
- Ensuring appropriate scientific assessment of access requests and proposed research use as well as management of COIs.
- Providing requested advice regarding publications and dissemination of research data that are potentially stigmatizing or discriminating to groups. Others, including the investigator, IRB, and possibly the groups studied, may share this responsibility.
- Educating the public and obtaining their feedback, where practicable, through the biospecimen resource's public Web site or alternate mechanism.

More specific recommendations by topic area are provided throughout this section.

C.1.1. Governance

Biospecimen resources should address formal and continuing responsibility for custodianship of collected biospecimens and associated data as part of their protocols. The following issues should be addressed in the governance plan: (1) How does the biospecimen resource propose to ensure the physical integrity of biospecimens? (2) How does the biospecimen resource propose to ensure the integrity of the human research participant data that accompany the biospecimens? (3) What plans and protocols are in place for the distribution of samples to investigators? and (4) What are the roles and responsibilities of the biospecimen resource director and his or her institution? (Also see [Section C.4](#), Access to Biospecimens and Data.)

C.1.2. Legacy or Contingency Plans

Biospecimen resources' legacy or contingency plans should be part of the overall governance plan and should address the handling and disposition of biospecimens and associated data at one or more of the following points: (1) End of the budget period of the grant, (2) loss of management or termination of funding, (3)

accomplishment of the specific research objectives of the study, (4) depletion of biospecimens, (5) achievement of critical data end points, and/or (6) discontinuation of participation by human research participants. At any of these points, an assessment of whether the stored biospecimens still have value for research should be conducted. If the stored biospecimens still have research value, the resource should consider whether to become financially self-sustaining. Alternatively, the resource should consider announcing the availability of the biospecimens for transfer to suitable research facilities by means appropriate for reaching a wide audience, if permitted by the informed consent document and the relevant IRB. Biospecimen resources should use the same decision making criteria for allowing transfer of biospecimens to other biospecimen resources as they do when allowing transfer of biospecimens to investigators. The transfer of such biospecimens should be consistent with human subjects regulations, the informed consent under which the biospecimens and data were initially collected, and any other prior agreements and institutional policies that may apply (Also see [Section C.2](#), Informed Consent.).

C.1.3. Policies on Retention

Biospecimen resources should establish and document transparent policies governing the retention of biospecimens and data. In addition, usage agreements, such as MTAs, should specify the retention policies of the recipient investigator. Other considerations related to biospecimen retention include the following:

- The retention of clinical biospecimens may be governed by Federal and/or State laws.
- For research biospecimens, permanent storage is generally preferred, subject to sufficient resources and storage space and foreseeable research utility; i.e., poor-quality biospecimens as determined via QA/QC processes should not be stored indefinitely.
- Biospecimen availability should be reviewed periodically (e.g., at the time of funding renewal) to determine the utility of the retained biospecimens and the need for new biospecimens.

C.1.4. Conflicts of Interest

Biospecimen resources, as responsible custodians, should manage existing or potential COIs and adhere to regulations regarding COIs at **42 CFR Part 50 Subpart F** [71], as well as other applicable regulations and policies (Also see [Section C.6.1](#), Investigator Financial Conflicts of Interest).

C.1.5. Confidentiality and Security

Biospecimen resources should implement transparent policies for maintaining the confidentiality and security of the biospecimens and associated clinical data, if applicable. Specifically, biospecimen resources that store coded samples and data should establish policies regarding how the link or code that allows identification of human research participants will be secured.

C.1.6. Public Communication

C.1.6.1

Where practicable, biospecimen resources should share the following general information with human research participants via their Web site or alternate mechanism:

- Whether biospecimens are shared with other researchers;
- How access decisions are made and what privacy protections are in place; and
- What general types of research studies are performed using biospecimens?

This information, or the corresponding Web link, should be included in the informed consent

C.1.6.2

A biospecimen resource should make public (e.g., on a Web site) a summary of its governance plan and/or an accompanying graphic of its organization.

C.2. Informed Consent

Informed consent pursuant to the human subjects regulations at **45 CFR Part 46 Subpart A** [72] is designed to present potential human research participants with sufficient information—including anticipated procedures, risks, and benefits—to make an informed decision about whether to participate in research studies. Obtaining informed consent for the collection, storage, and future research use of biospecimens can be challenging because the specifics of the future research often are not known at the time of biospecimen collection. Additional considerations arise when consent is sought for biospecimen research involving the use or generation of genomic data (See the NIH National Human Genome Research Institute (NHGRI) website [73]). But under certain conditions, research involving the use of previously collected biospecimens and/or data may not be considered human subject research requiring informed consent. In addition (See OHRP guidance [74]), under DHHS regulations at **45 CFR Part 46 Subpart A** [72] informed consent may not be required even if the research is considered human subjects research if (1) the human subjects research is exempt from the regulations at **45 CFR § 46.101(b)** [75] or (2) the research is nonexempt human subjects research that has been granted a waiver of the requirements for informed consent by an IRB under **45 CFR § 46.116(c) or (d)** [76].

C.2.1. Federal Regulations and Guidelines Pertaining to Informed Consent

C.2.1.1.

DHHS-conducted or -supported research on human research participants is regulated by **45 CFR Part 46** [70].

The DHHS regulations describe both when informed consent is required and what elements must be in an informed consent process and document. The biospecimen resource should track whether appropriate informed consent is present or the reason why informed consent is not necessary and should seek to resolve any discrepancies in the consent status for stored biospecimens (See the Office for Human Research Protections [OHRP] Web site for guidance on informed consent [77]).

C.2.1.2.

The OHRP has issued guidance on regulatory requirements that must be satisfied by biospecimen resources (available at [78]). The OHRP recommends that the following be included in informed consent documents for biospecimen collection:

- A clear description of the operation of the biospecimen resource. This description could include details that may be of interest to human research participants, such as whether identifiable information will be maintained by the biospecimen resource and/or whether research results will be linked to the biospecimen (See [Section C.1](#), Principles for Responsible Custodianship, for NCI recommendations).
- The conditions under which samples and data will be released to recipient investigators (See [Section C.4](#), Access to Biospecimens and Data, for NCI recommendations).
- Procedures for protecting the privacy of human research participants and confidentiality of data (See [Section C.3](#), Privacy and Confidentiality Protections, for NCI recommendations).
- Specific descriptions of the nature and purpose of the research.
- Information about the consequences of DNA typing if human genetic research is anticipated. NHGRI has developed an online Web resource with the goal of providing the research community with the information needed to develop informed consent materials for genomics-related research projects, such as genome-wide association studies (GWAS) and gene sequencing studies. See the NHGRI online consent information Web resource [79].

C.2.1.3.

FDA regulations regarding informed consent should be considered when applicable, particularly when human specimens are used for *in vitro* diagnostic device studies (See 21 CFR Part 812 [80], 21 CFR Part 50 [81], and 21 CFR Part 56 [82]). The FDA may exercise enforcement discretion as to the requirement for informed consent for *in vitro* diagnostic device studies that utilize “leftover” biospecimens (e.g., remnants of biospecimens collected for routine clinical care or analysis or biospecimens previously collected for another research purpose) that are not individually identifiable if certain conditions have been met.³

C.2.1.4.

For samples collected on or after the effective date of the NIH GDS Policy (January 25, 2015), NIH expects that research participants have given consent for their genomic and phenotypic data to be used for future research purposes and shared broadly, in order for the data to be submitted to an NIH-designated repository. Consent is required even for cell lines or clinical samples which are de-identified. If there is consent which is not consistent with the NIH GDS Policy, then the samples cannot be used for research falling under the Policy unless an exception applies. NIH Guidance on the GDS Policy consent requirements are available: [83]

The NIH GDS Policy consent requirements are consistent with the NCI Best Practices at C.2.3 that informed consent address:

- How the biospecimens will be used and whether they may be used in secondary research.
- How data collected or generated in the research will be shared.
- Who may access biospecimens and associated data, including whether for-profit research may seek access.

The NIH GDS Policy endorses biospecimen resources utilizing a “one-time general consent” strategy [see C.2.3.9].

C.2.2. General NCI Recommendations Pertaining to Informed Consent

The extent to which a biospecimen resource is involved in the informed consent process varies widely and depends on the mission of the resource. Many biospecimen resources collect biospecimens and participate in the informed consent process whereas others store biospecimens originally collected for alternate purposes or by researchers not affiliated with the resource. Regardless of the level of involvement in the informed consent process, biospecimen resources should ensure that the research uses of biospecimens are consistent with the informed consent of the human research participant.

C.2.2.1.

The NCI recommends seeking the informed consent of research participants who provide biospecimens and associated data whenever such consent is required by regulation, and also when consent is ethically appropriate and can practicably be obtained. Respect for individuals who have provided data and/or biospecimens for research is of paramount importance; therefore, their preferences should be considered when deciding whether informed consent should be sought or waived. Some individuals may prefer to be actively engaged in future research, while others may be opposed to being re-contacted to consent for additional research or future uses. The biospecimen resource should have transparent policies concerning the informed consent process, including when consent is sought from human research participants or from the next of kin of deceased biospecimen contributors. Electronic consent (e-consent) or mobile consent

³ Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens That Are Not Individually Identifiable. Available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm078384.htm>.

strategies may streamline the consent process and improve participant understanding of consent information.

C.2.2.2. Personal, religious, and culturally held beliefs and traditions should be respected in biomedical research using biospecimens. For example, some cultures believe that the body is sacred and should not be disturbed [84, 85]. Investigators should consider the beliefs and traditions of the community when planning a research study that will include collection of biospecimens and whether any of the following issues should be addressed for the population under study during the informed consent process:

- Whether there are any religious, cultural, or personal restrictions regarding the biospecimen.
- What are the instructions for disposal or return, if practicable, of the biospecimen?
- What is the participant's primary language and whether the consent is explained in that language?

The biospecimen resource should track any relevant restrictions or instructions based on these types of beliefs in order to ensure that the human research participant's wishes are upheld.

C.2.2.3.

For biospecimens collected during the course of medical care, the timing of consent (e.g., before or after a medical procedure) to use biospecimens for research purposes should not be imposed rigidly but instead informed by a number of important considerations, including ethical guidelines and logistical constraints.

Generally, consent should be obtained prior to the medical procedure, but post-medical procedure consent may be appropriate in some circumstances [86]. These decisions should be made on a case-by-case basis with sensitivity to the situation a patient faces when undergoing a medical procedure or a test for a serious disease. For example, post-medical procedure consent may be acceptable for the use of remnant biospecimens beyond what is needed for diagnostic purposes if it was not practicable to previously consent the patient because of considerations about illness, undue stress, or the ability of the patient to fully comprehend what was being asked. However, prior informed consent would be required in cases where biospecimens are collected from human research participants for research purposes or when the procedure for collecting biospecimens for clinical purposes is changed to meet a research need unless an IRB grants a waiver of the requirements for obtaining informed consent.

C.2.2.4.

Information about policies governing the retention of biospecimens, placement of research data in clinical records, documentation pertaining to informed consent, and protections for the privacy of human research participants and the confidentiality of their data should be provided to participants either in the informed consent document or in supporting materials (Also see [Section C.1](#), Principles for Responsible Custodianship).

C.2.2.5.

The informed consent document should disclose whether biospecimens may at some point be de-identified and/or subsequently used for secondary research purposes beyond those described in the original informed consent. Human research participants deciding whether to contribute biospecimens for research should understand how their tissue may be used in the future, including any potential anonymous use. The NIH GDS Policy requires that data submitted to an NIH-designated repository be de-identified according to standards set forth under the regulations for the protection of human subjects at 45 CFR 46, as well as the requirements of the HIPAA Privacy Rule. In addition, NIH has obtained a Certificate of Confidentiality as an additional precaution because genomic data can be re-identified.

C.2.2.6 New concepts that strengthen the informed consent process by facilitating community engagement in the research are under development and being piloted. These efforts include biospecimen resource

community advisory boards, community consultation, and community based participatory research projects. These governance models [87-89] view participants as partners in the research and promote the underlying ethical values of informed consent, including respect and autonomy.

C.2.3. NCI Recommendations on Key Informed Consent Elements and Supplementary Materials

The list of elements in this section is provided to guide and inform biospecimen resources about important ethical and policy issues relevant to the informed consent document. The informed consent document for the collection and future research use of biospecimens should balance the requirement to provide sufficient information to human research participants to make an informed decision with the need to ensure that the document is comprehensible and reasonable in length. The elements listed below may be adapted depending on the nature of the resource and its mission.

C.2.3.1.

For the benefit of human research participants, an informed consent document outlining important issues and risks in straightforward language should be developed and implemented. The informed consent document should specify the following:

- That patients have the right to refuse biospecimen donation, and that this will in no way influence their treatment or eligibility to participate in research studies or clinical trials.
- Why particular biospecimens and data are being sought and why human research participants are being asked to participate.
- The source of the biospecimens that will be collected for research; for example, whether the biospecimen will come from leftover tissue from a surgical procedure or from an additional procedure (e.g., an extra blood draw).
- Who will be the custodian of the biospecimens and what will be the custodian's role.
- How the obtained biospecimens will be used and whether they may be used in secondary research.⁴
- How data collected or generated in the research will be shared.
- Whether biospecimens will continue to be stored in an identifiable or non-identifiable manner, and shared as long as they are potentially useful for research, respectfully destroyed when no longer useful for research, or transferred to another established resource in accordance with the terms of the informed consent.
- Who may access biospecimens and associated data, including whether for-profit researchers may seek access and, if so, any policies regarding disposition of potential commercial profits.
- Whether there is a policy or plan for producing a lay summary of the aggregate study findings.
- Whether there is a policy or plan for offering the return of any individual research results, and whether these results will be placed in the medical record.
- The nature of any special risks associated with proposed genomic research technologies such as whole genome or exome sequencing

C.2.3.2.

The informed consent document should describe what types of data will be collected and how the data will be used and stored. Where applicable, the informed consent document should state whether identifiable or coded information will be maintained in the biospecimen resource and if research results will be linked to

⁴ "Secondary research" is defined as any other research use beyond the scope of the primary study.

other data about the human research participant, such as clinical data obtained from anatomic pathology and clinical pathology laboratory information systems and cancer registries (Refer to [Section B.5.3](#), Longitudinal Clinical Data, for further recommendations on the integration of informatics systems). If longitudinal data will be collected by accessing the participant's medical records, the informed consent document should clearly state this. The informed consent document also should describe whether the biospecimens and/or the data associated with or derived from biospecimens will be shared with other investigators and, if so, the oversight mechanisms for such sharing.

C.2.3.3.

If appropriate, the informed consent document may include an option that allows human research participants to select whether they would be willing to be re-contacted about the use of their biospecimens and/or data in future research studies.

C.2.3.4.

The informed consent document should state whether research participation could benefit or potentially negatively impact participants' families and communities; e.g., if there is a risk of stigmatization and discrimination based on research results.

C.2.3.5.

If a study involves genetic sequencing or analysis, the informed consent document should include information about the types of genetic sequencing or analysis that will be conducted (e.g., somatic, familial, or whole genome analysis) and the potential risks to the human research participant posed by such research, if applicable. NHGRI has several consent form examples and model consent form language [\[90\]](#). The Genetic Information Nondiscrimination Act (GINA, [\[91\]](#)) of 2008 may reduce some of these risks by prohibiting employment and health-insurance discrimination on the basis of genetic information. GINA does not protect against potential discrimination on the basis of genetic information for disability or long-term care insurance. For more information on GINA, please refer to the guidance from the OHRP [\[92\]](#) and the discussion of genetic discrimination and GINA on the NHGRI website [\[93\]](#).

C.2.3.6.

The informed consent document should address the use of biospecimens and/or data by private or for-profit entities and the possibility of research leading to future development of commercial products, as appropriate. The document should describe whether human research participants, their families, or communities will receive any financial or nonfinancial benefits from the products, tests, or discoveries resulting from the research.

C.2.3.7.

The informed consent document should state whether individual or aggregate research results will be released to the human research participant, the participant's healthcare provider, or the participant's family and, if so, the mechanism for communicating such results; e.g., e-mail, newsletter, telephone call, genetic counselor, etc. Individual research results may range from primary diagnostic findings or discrepancies to secondary "incidental" findings unrelated to diagnosis or even to study aims. Any procedure for opting out of the receipt of research results should be clearly indicated. The HIPAA Privacy Rule [\[94\]](#) and the Clinical Laboratory Improvements Amendments (CLIA, [\[95\]](#)) may affect whether research results should be offered or disclosed.

NCI recommends that in developing policies pertaining to the return of individual research results, institutions consider whether these findings are analytically validated, medically significant, and clinically actionable to research participants and/or their relatives.

C.2.3.8.

General information about COIs, institutional policies for sharing samples with other investigators or companies, the financial implications of sharing, and any known or likely benefit to the institution or investigator should be easily found online at the resource's or institution's Web site or provided in a brochure that accompanies the informed consent document (Also see [Section C.6](#), Conflicts of Interest).

C.2.3.9.

Biospecimen resources may utilize a “one-time general consent” strategy [96] whereby biological specimens and data are collected for broad use in future research studies that will subsequently be approved by institutional review boards or other panels of scientific and ethical experts.

C.2.3.10.

A tiered system of consent may be considered where human research participants could specify the types of research for which their contributed biospecimens will be used.

While a tiered system of consent will provide the human research participant with greater specificity about secondary research, it also can lead to ambiguities in terms of how to classify certain types of interdisciplinary or multidisciplinary research. If the purpose of the biospecimen resource is to provide biospecimens for a broad range of research, tiered consent may be burdensome and uninformative. Tiered consent may be considered if consent categories are well defined and relatively constant over time and if an informatics system capable of tracking the levels of consent for each human research participant is already in place. Whenever tiered consent is utilized, biospecimen resources should adhere to the human research participant's choices in order to ensure that his or her wishes are honored.

Examples of tiered consent categories are as follows:

- My tissue may be kept for use in research to learn about, prevent, or treat cancer.
- My tissue may be kept for use in secondary research to learn about, prevent, or treat other health problems; e.g., diabetes, Alzheimer's disease, or heart disease.
- My tissue may be associated with my medical record and history.
- I am willing to be contacted about future research studies.

C.2.3.11.

Biospecimen resources should consider whether, in addition to the informed consent document, more detailed supplementary materials should be made available to interested human research participants. If supplementary materials are provided, protocols should be in place to ensure that such materials are consistently offered to human research participants and that the content does not conflict with the informed consent document. These materials may include the following:

- A one-page graphic or written summary outlining the biospecimen resource's governance, with an emphasis on oversight and access protocols.
- An accompanying brochure that provides more detailed information about the biospecimen resource, either directly or by referencing the resource's Web site, and covers any other issues that could not be addressed in the informed consent document.

C.2.4. Issues Pertaining to Discontinuation of Participation in Research

Biospecimen resources should develop policies for responding to requests for discontinuation of participation in research, consistent with OHRP⁵ and [FDA guidance](#).⁶ Participation in research includes the collection of

⁵ Guidance on Withdrawal of Subjects from Research: Data Retention and Other Related Issues, released September 21, 2010.

biospecimens or of individually identifiable private information from human research participants (even if the investigator does not personally interact or intervene with the participant) and the use, testing, or analysis of biospecimens or information already collected. The informed consent document should highlight the human research participant's ability to discontinue participation in research and describe what will take place should this occur. In turn, biospecimen resources should develop SOPs related to how a request to discontinue participation in research will be handled, including processes to verify that the SOP was followed and mechanisms for annotating that a discontinuation event occurred.

- Discontinuation of participation in research may be complete or partial. In some cases, the human research participant may wish to discontinue some elements of the research project, such as activities involving intervention or interaction, but may want other activities to continue, such as further testing and analysis of biospecimens already collected. When a human research participant seeks to discontinue participation in medical research that has included collection of biospecimens and associated clinical data, the custodian or resource's director should determine whether the withdrawal is limited to future interventional and/or interactional activities, or is a full and complete discontinuation of participation.
- When a human research participant discontinues participation in research, further collection and distribution of biospecimens or associated clinical data for research purposes should cease. In addition, if the withdrawal applies to previously stored biospecimens and associated clinical data, the biospecimen resource should not distribute for further research any remaining stored biospecimens or associated data. However, analysis of data, generated from biospecimens distributed to researchers prior to the date of discontinuation of participation may occur, provided that such analysis falls within the scope of the analysis described in the IRB-approved protocol.
- If a human research participant who is discontinuing participation in research requests that previously stored but unused biospecimens be destroyed, biospecimen resources and recipient investigators, if applicable, should respect that request. The consent document should clarify whether it is the policy of the biospecimen resource to destroy biospecimens in the event of a human research participant's discontinuation of participation in research.
- With respect to any request for removal of data from a biospecimen resource by a research participant who is discontinuing participation, clinical trial study participants may be prevented from removing their stored data from a biospecimen resource if such removal would compromise the scientific validity of the study. In considering any request to purge stored data, biospecimen resources should consider whether such action would undermine the integrity of data collected from other human research participants who made an informed choice to contribute biospecimens to research. Biospecimen resources should be sensitive to cultural issues and work with affected groups to develop mechanisms for the proper destruction of biospecimens or, as appropriate and practicable, the return of biospecimens to the individual or affected group (see [Section C.2.2](#)).

C.2.5. Considerations for Use of Pediatric Biospecimens

Biospecimen resources that store identifiable biospecimens and/or identifiable data from children for future research use should consider the need for obtaining informed consent when the formerly pediatric human research participant reaches the legal age to consent for a research study. Under **45 CFR 46 [70]**, activities that involve the use of identifiable biospecimens and/or associated identifiable medical data constitute human subjects research and would therefore require investigators to seek and obtain the legally effective informed consent of the now-adult participants.⁷ However, the IRB may consider whether a waiver of informed consent

⁶ Guidance for Sponsors, Clinical Investigators, and IRBs: Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials, released October 2008

⁷ See the OHRP frequently asked questions related to this topic at: <http://answers.hhs.gov/ohrp/categories/1566>.

under **45 CFR 46.116(d)** [76] is appropriate. In addition, the following operational best practices related to this issue should be considered when developing a biospecimen resource:

- Biospecimen resources that plan to store identifiable biospecimens from children should consult with their IRB during planning and development of the resource to determine whether future research uses of stored biospecimens are likely to constitute no more than minimal risk. If future uses of identifiable stored biospecimens are likely to constitute greater than minimal risk, biospecimen resources should develop procedures for recontacting human research participants to obtain consent at the age of majority and ensuring that accurate contact information is maintained. Where practicable, human research participants should be recontacted for consent by an individual or institution with which they have an ongoing relationship.
- Permission and/or assent documents for contribution of pediatric biospecimens for research should state whether recontact and consent will be attempted once the child reaches the age of majority.
- Community engagement should be considered when planning a biospecimen resource that will store identifiable biospecimens and/or data from children, if appropriate. Community engagement may range from public forums to inclusion of patient advocates or community representatives on access or governance committees. As part of biospecimen resource planning activities, input from the affected community may be sought in regard to the perceived risk-benefit ratio of the proposed research and whether a waiver of consent or consent at age of majority would be preferable. Community engagement may be unnecessary or inappropriate in some cases, such as for the use of archived biospecimens or for minimal-risk research.
- Unique Considerations for Biospecimen Resources that Collect and/or Distribute Newborn Blood Spots. A federal law enacted in December of 2014 considers federally funded research involving newborn blood spots, whether de-identified or identifiable, to be research involving human subjects which requires informed consent. The law does not apply to retrospective collections but affects federally funded research involving newborn blood spots collected as of March 16, 2015.

C.3. Privacy and Confidentiality Protections

Biospecimen research depends on protecting the privacy of individuals who contribute biospecimens and on maintaining the confidentiality of associated clinical data and information [97]. Applying the highest possible ethical standards is necessary to ensure the support and participation of human research participants, physicians, researchers, and others in biospecimen resource activities. With the recent advances in genomic and proteomic technology, the sequencing of the human genome, and the increasing reliance of biospecimen resources on electronic and Web-based databases for data tracking, it is even more crucial to address the risk of breaches in privacy. The unintended release or disclosure of sensitive information can place individuals at risk for discrimination and related groups at risk for stigmatization although the frequency of these types of harms is unknown.

C.3.1. Federal Regulations Pertaining to Privacy

The DHHS-issued regulation titled “Standards for Privacy of Individually Identifiable Health Information,” commonly known as the HIPAA Privacy Rule (see **45 CFR Part 164** [98] and **Subparts A and E of Part 160** [99]), was created to protect the privacy of health information that identifies an individual while still allowing other activities of benefit to society, such as research. While the HIPAA Privacy Rule does not apply to biospecimens directly, it may affect biospecimen resources that are considered covered entities, or business associates of covered entities, in that human specimens often are accompanied by identifiable protected health information (PHI). For more information on the application of the HIPAA Privacy Rule to research repositories and databases, see [100]. If the biospecimen resource is considered a covered entity under HIPAA, compliance with the regulation titled “Security Standards for the Protection of Electronic Protected Health Information,” commonly known as the Security Rule, is required to ensure appropriate

security of electronic PHI (see **45 CFR Part 160 and Part 164 Subparts A and C** [[98](#), [99](#)]). Detailed information on the HIPAA Security Rule is available at [[101](#)].

In January of 2013 the US Department of Health and Human Services issued an Omnibus Final Rule implementing amendments to HIPAA enacted under legislation known as HITECH (Health Information Technology for Economic and Clinical Health). The HITECH amendments to HIPAA contain several provisions affecting research involving biospecimens and the creation of biospecimen resources for future research. The rule was published in the Federal Register and is available at [[102](#)].

Under the NIH Genome Data Sharing (GDS) Policy [[69](#)], any restrictions on participant consent for future research uses of data must be captured in the data use limitations that accompany the data when it is submitted to an NIH-designated repository, via the institutional certification process [[103](#)] [see also below].

C.3.2. NCI Recommendations Pertaining to Privacy and Confidentiality

C.3.2.1.

Biospecimen resources should establish clear policies for protecting the confidentiality of identifiable information. These policies may include data encryption, coding, establishing limited access or varying levels of access to data by biospecimen resource employees, and use of nondisclosure agreements. An honest broker–guided procedure, if appropriate, should be considered for sharing of samples and data to protect research participants’ privacy [[104](#), [105](#)]. The informatics system and not necessarily an individual can function as the honest broker.

C.3.2.2.

Biospecimen resources may apply for “certificates of confidentiality” to protect identifiable research information from forced disclosure. Under section 301(d) of the Public Health Service Act [[106](#)](42 USC 241(d)), the NIH may issue certificates of confidentiality to authorize persons engaged in biomedical, behavioral, clinical, or other research to refuse to disclose identifying information about human research participants in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding. Certificates of confidentiality should be considered by the biospecimen resource and/or the recipient investigator depending on the nature and sensitivity of the identifiable data associated with the biospecimen. Certificates of confidentiality may not be appropriate for all biospecimen resources. If a certificate of confidentiality is obtained, this should be explicitly stated in the informed consent document. Further information about certificates of confidentiality may be found at [[107](#)].

C.3.2.3.

Biospecimen resources should document their policies for maintaining the privacy of human research participants and the confidentiality of associated clinical data, including descriptions of mechanisms for auditing effectiveness, enforcement measures, agreements not to release code keys or not to attempt re-identification of individuals from de-identified data (see database of Genotypes and Phenotypes (dbGaP) Code of Conduct [[108](#)]).

The level of security should be appropriate to the type of biospecimen resource and the sensitivity of the data it houses. Genetic data, in particular, may involve additional risks such as discrimination and/or stigmatization, and these concerns may have an impact on research participants’ families or broader population groups. De-identification of research data cannot completely guarantee privacy given the growth in publically available and electronically shared databases, as well as evolving technologies for linking different types and sources of data [[109-111](#)]. Respect for research participants requires transparency about

the tradeoffs between limiting access to individual medical data and facilitating the greatest utility of such data in research.

C.3.2.4.

Biospecimen resources should comply with all applicable State and local statutes and regulations pertaining to privacy. Biospecimen resources that collect, store and/or distribute large scale human or non-human genomic data derived from NIH-funded research should comply with the relevant mandates of the NIH Genome Data Sharing Policy [69].

C.3.2.5.

Biospecimen resources should use a system of data access with defined levels of access privileges for biospecimen resource staff in order to protect the confidentiality of human research participants' data, if necessitated by data type and sensitivity.

- Access levels for biospecimen resource staff should be described in the protocol for operation of the biospecimen resource and approved by an IRB and/or a bioethics/scientific advisory board, as appropriate.
- Access to human research participants' identities and medical, genetic, social, and personal histories should be restricted to only those biospecimen resource staff members who need to access such records as part of their assigned duties or to those persons permitted access by law.
- The number of personnel allowed to access links and reidentify information should be kept to a minimum, and access should be appropriately monitored to ensure compliance.

C.3.2.6.

Data submitted to an NIH-designated repository under the GDS Policy [69] must be de-identified according to standards set forth under the regulations for the protection of human subjects at 45 CFR 46, as well as the requirements of the HIPAA Privacy Rule. In addition, NIH has obtained a Certificate of Confidentiality for dbGaP as an additional precaution because genomic data can be re-identified.

These GDS Policy elements should be discussed in the informed consent, consistent with NCI recommendations that the informed consent disclose whether biospecimens may at some point be de-identified [see C.2.2.5], and that if a certificate of confidentiality is obtained, this should be explicitly stated in the informed consent document [see C.3.2.2].

C.4. Access to Biospecimens and Data

Timely access to human specimens and data is crucial for research fields such as genomics, proteomics, metabolomics, molecular imaging, and nanotechnology. Researchers in these areas often rely on federally funded biospecimen resources for high-quality biospecimens and associated data. To best serve the needs of the research community, biospecimen resources should establish guidelines for sample distribution and clinical data sharing consistent with ethical principles; governing statutes and regulations; and, if applicable, informed consent language. These guidelines should have the following characteristics:

- *Clear* to ensure their comprehension and adoption;
- *Flexible* to allow application to diverse and evolving scientific needs; and
- *Amendable* to facilitate their adaptability over time.

In addition, the guidelines established by biospecimen resources should delineate when biospecimens and clinical data are narrowly or broadly accessible and what justifications should be provided in the access requests to the biospecimen resources. These guidelines should apply to all new collections and, whenever practicable, to existing collections.

Under the NIH Genome Data Sharing Policy [69] human data in an NIH-designated repository is available to the broader scientific community under controlled-data access (unless otherwise specified, consistent with participant consent). Requests for controlled-access data are reviewed by an NIH Data Access Committee (DAC), and are granted based primarily on whether the proposed research use is consistent with the data use limitations (which are based on the informed consent of participants). NIH DACs do not review for the scientific merit of proposed research to use data in the NIH-designated repository. Investigators granted access to data in an NIH-designated repository must comply with the terms and conditions for the use of the data as set for in the Model Data Use Certification Agreement [112]. Accessing investigators must also abide by National Center for Biotechnology Information security best practices [113]. Information about access under the NIH GDS Policy should be included in the informed consent, consistent with NCI recommendations that the informed consent document describe whether data associated with or derived from biospecimens will be shared with other investigators and, if so, the oversight mechanisms for such sharing [see [Section 2.3.2](#)].

C.4.1. General Principles for Access Decisions

Access decisions should be guided by the following general principles, as appropriate:

- Timely, equitable, and appropriate access to human specimens without undue administrative burden.
- Scientific merit and institutional research qualifications, proven investigator experience with the proposed method, and a research plan appropriate to answer the study question.
- Community attitudes and ethical/legal considerations as primary factors.
- Fair, transparent, and clearly communicated access procedures.
- Appropriate allocation of biospecimens based on the nature of the scientific investigation (e.g., discovery, prevalence, initial validation, and hypothesis testing) and the need for annotation. The level of identifiability of the biospecimen and related transfer documents should be appropriate for the proposed research.
- A mechanism for addressing disputes over allocation decisions.
- An investigator agreement covering confidentiality, use, disposition, and security of biospecimens and associated data.
- The parties' written agreement in an MTA or other appropriate document that is consistent, as applicable, with the NIH Research Tools Policy [114] and other applicable NIH sharing policies [68].

C.4.2. Research Plan

A scientifically sound and appropriate research plan should be included in access requests. If applicable to the study design and biospecimen resource purpose, the following specific issues are among those to be considered by the biospecimen resource in access decisions:

- Use of standardized, validated research biomarker assay methodology.
- Statistical evaluation that shows that the study question can be addressed with the samples available and, if applicable, a negotiated arrangement with a clinical protocol coordinating group to provide timely statistical analysis of study results.
- Compliance with protocol-specific requirements needed to achieve study goals before other access is considered.

- Confirmation that an investigator has defined funding and IRB approval for the project, if applicable (for information on application for and exemption from IRB approval, see OHRP guidance [\[115\]](#)).
- Agreement that the investigator will publish or provide public information about the project outcome according to applicable NIH policies, which may include the Research Tools Policy, and the Revised Policy on Enhancing Public Access to Archived Publications Resulting from NIH-Funded Research [\[116\]](#) (see: [\[117\]](#) and the 2013 update to the policy [\[118\]](#)). Of note, the NIH Research Tools Policy permits reasonable short-term publication delays; e.g., to file a patent or allow a collaborator to review a manuscript.

C.4.3. Access Policies

Appropriate policies should be developed to ensure that researchers' access to biospecimens and associated clinical data is appropriate and in compliance with all applicable Federal and State privacy and human subjects regulations and statutes as well as the human research participant's informed consent. The following issues should be considered when developing access policies:

- Inclusion of appropriate provisions for the security of biospecimens and confidentiality of associated data in the usage agreement between the biospecimen resource and the researcher. For OHRP guidance on the use of coded biospecimens and data, see [\[74\]](#).
- Consistency of the MTA or other appropriate document, as applicable, with the NIH Research Tools Policy [\[114\]](#) and other applicable NIH sharing policies [\[68\]](#).
- Development of an informatics system to facilitate use or disclosure of biospecimens consistent with the research participant's permission for the use of his/her biospecimens, including procedures to identify if and when that research participant has revoked consent for future research use.

C.4.4. Models of Sustainability

Appropriate models of biospecimen resource sustainability should emphasize accessibility to biospecimens and data and sustainability of the biospecimen resource within a framework that maintains public trust. These models should account for potential loss of funding; i.e., a legacy plan should be in place. (Also see [Section C.1.2](#).) For example, in a cost-recovery model, charges for samples, if any, are used only to recover reasonable costs associated with operation of the biospecimen resource and not to generate undue profit for the biospecimen resource. Biospecimen resource sustainability models other than cost recovery (e.g., a collaborative agreement model involving more than one approved funding partner) may also be considered to support a biospecimen resource over the long term. NCI has developed a publicly available Biobank Economic Modeling Tool to aid in cost recovery and financial planning for biobanking, available online at (BEMT link: [\[16\]](#)). Note that receipt of Government funding, regardless of other financial sources, results in the expectation that biospecimens and resulting research resources and data will be available, consistent with applicable NIH sharing policies [\[68\]](#).

C.4.5. Availability of Biospecimens

The existence of biospecimens may be made public through the resource's Web site itself and/or through well-known resources such as the NCI Specimen Resource Locator [\[67\]](#), which serves as a directory of biospecimen resources. Restrictions on accessibility to stored biospecimens should be indicated in these tools. In addition, biospecimen resources should encourage investigators to indicate the source of the biospecimens when research data resulting from the use of biospecimens are published.

C.5. Intellectual Property and Resource Sharing

Inventions and data arising from research using annotated biospecimens may have commercial value. As researchers and industry sponsors have sharply increased their demand for properly prepared and clinically annotated biospecimens, some institutions have begun to assert control over biospecimens, associated data, and

research findings. The current variability in intellectual property (IP) policies at institutions hosting research and biospecimen resources may ultimately lead to problems in biospecimen and data access, timely and open publication, sharing of research findings, and establishment of new biospecimen resources. Sharing of research data obtained through use of biospecimens and associated research materials (e.g., derivatives) is essential for the advancement of science. Accordingly, research data and tools generated through the use of biospecimens should be shared in a timely manner and, to the greatest extent possible, in a manner consistent with applicable NIH sharing policies.

C.5.1. Material Transfer Agreements

An agreement (e.g., MTA or contract) with terms consistent, as applicable, with the NIH Research Tools Policy, the NIH Data Sharing Policy, and other applicable NIH sharing policies should be used for the transfer of materials among academic, nonprofit, and/or industrial organizations (see [Appendix 4](#) for a sample MTA). Clinical protocols are not designed to document material transfers and are usually inappropriate for this purpose. Examples of agreements that capture the basic principles of the NIH policies above are the NIH Simple Letter of Agreement and the Uniform Biological Material Transfer Agreement [119]. However, these agreements are insufficient for the transfer of human specimens without appropriate modification. Desirable terms in an MTA for the transfer of biospecimens include the following:

- Clear descriptions of the biospecimens and/or unmodified functional derivatives thereof (e.g., DNA and RNA) and identification of the institutions involved;
- Clear identification of the human subjects status of the biospecimens and associated obligations;
- Specific assurance that the biospecimen source site obtained appropriate informed consent and IRB approval;
- Agreement to abide by appropriate laws, rules, and regulations associated with human subjects research and private information;
- Acknowledgement of the recipient's right, or lack thereof, to further distribute the biospecimens;
- Assurances of the end user's academic freedom and the right to publish research results will not be hindered by the biospecimen resource; IP terms consistent with, as applicable and permissible, the basic principles of the NIH Research Tools Policy and other applicable NIH sharing policies, such as no reach-through by the biospecimen resource to end users' IP and the sharing of research resources and data by the end-user with the research community;
- Description of any expectations regarding the dissemination of research data; and
- Conditions, or limitations, on commercial use, if any.

The following Web pages are relevant to this issue:

- <http://sharing.nih.gov>
- http://grants.nih.gov/grants/intell-property_64FR72090.pdf
- <http://www.autm.net/resources-surveys/material-transfer-agreements/uniform-biological-material-transfer-agreement/>
- http://grants.nih.gov/grants/policy/data_sharing/

C.5.2. Inventorship

Generally, biospecimen resource staff, as custodians of biospecimens, will not be considered a priori inventors under patent law for inventions made using materials distributed by the biospecimen resource. In general, one whose sole contribution to an invention consists of the routine collection, handling, storage, and disbursement of biospecimens might not rise to the level of "inventor." Inventorship is determined by patent law and is considered on a case-by-case basis by legal personnel.

C.5.3. IP Rights

Generally, biospecimen resources have no inherent rights to future IP of end-users, such as reach-through rights to inventions made by investigators using samples obtained from the biospecimen resource.

C.5.4. Licensing

When IP resulting from biospecimen research is exclusively licensed, a research use license should be retained that allows nonprofit and Government research use and ensures access to resources and data for research and educational purposes.

C.5.5. Data and Resource Sharing

Through MTAs or other appropriate documents, research data and research resources obtained using biospecimens should be made available to the research community to the greatest extent possible, consistent with, as applicable, the NIH Data Sharing Policy [68], the NIH Genomic Data Sharing Policy [69], other applicable NIH sharing policies, [68] and the NIH Research Tools Policy [114]. Consistent with the applicable NIH policies, completed data sets and resources should be released in a timely fashion; i.e., no later than acceptance for publication of the main findings from the final data set. To promote future biomedical research, data and resources developed with biospecimens would be retained only as long as necessary for legitimate and imminent research purposes. Information that is identifiable or linked to a specific individual should be shared under an agreement with appropriate privacy safeguards and adherence to applicable legal requirements. A reasonable delay to ensure an investigator's publication priority or to secure IP protection is acceptable. See Section [C.6. Conflicts of Interest](#)

A financial COI exists, according to Public Health Service (PHS) regulations, when a designated institutional official(s) reasonably determines that an extramural Investigator's significant financial interest could directly and significantly affect the design, conduct, or reporting of PHS-funded research (42 CFR Part 50, Subpart F and 45 CFR 94). An Investigator is defined by these regulations as the principal investigator and any other person who is responsible for the design, conduct, or reporting of research funded by PHS or proposed for such funding. Generally, it is the awardee institution that is responsible for maintaining compliance with the requirements of the regulations, identifying and managing Investigator Financial Conflicts of Interest and reporting them to the PHS-awarding component. Investigators disclose their Significant Financial Interests, as defined in 42 CFR § 50.603 and 45 CFR § 94.3, to their institutions. Significant Financial Interests include those of an investigator's spouse and dependent children. Extramural investigators conducting biospecimen research activities supported by PHS grants, cooperative agreements, or research contracts are subject to the requirements of these regulations (see the NIH Office of Extramural Research [120] Web site for more information on COIs). Federal employees are subject to different regulations related to COI, as described in 18 USC 208, the Standards of Ethical Conduct for Employees of the Executive Branch, and agency-specific regulations (see the NIH Conflict of Interest [121] Web site for more information related to federal employees).

C.6. Conflict of Interest

C.6.1. Investigator Financial COIs

The regulations governing extramural research contain examples of conditions or restrictions that might be imposed by an awardee institution to manage Investigator financial conflicts of interest, which includes public disclosure of a significant financial interest. The responsibility of COI management rests with the awardee institution as described in the regulations. Awardee institutions and Investigators should adhere to institutional and PHS regulations governing COIs.

C.6.2. Institutional Financial COIs

Institutional financial COIs should be considered and managed as appropriate. Any known or likely financial benefit to the institution or biospecimen resource should be disclosed accordingly, for example on the

biospecimen resource Web site or in a clear and concise manner in a brochure that accompanies the informed consent document (Also see [Section C.2.3](#), NCI Recommendations on Key Informed Consent Elements and Supplementary Materials).

C.6.3. *Nonfinancial COIs*

Nonfinancial COIs should be identified and managed to the extent practicable. An example of a nonfinancial COI includes situations in which the individual managing the biospecimen resource is also a researcher seeking access to biospecimens. In cases where nonfinancial COIs are unavoidable (e.g., small biospecimen collections), biospecimen resources should manage the COIs by adhering to NIH policies and, if deemed necessary, publicly disclosing the COIs; e.g., via the resource's Web site or written materials.

Web Resources⁸

Biological Material Transfer Agreement

Uniform Biological Material Transfer Agreement Federal Register

<http://www.bioinfo.com/ubmta.html>

Code of Federal Regulations

Government Printing Office Access

<http://www.gpo.gov/fdsys/browse/collectionCfr.action?collectionCode=CFR>

Conflict of Interest

Conflict of Interest, NIH Office of Extramural Research

<http://grants.nih.gov/grants/policy/coi/>

Conflict of Interest Information and Resources, NIH

http://www.nih.gov/about/ethics_COI.htm

Electronic Records and Electronic Signatures

Electronic Records; Electronic Signatures

Office of Regulatory Affairs, U.S. Food and Drug Administration

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11&showFR=1>

Health Information Portability and Accountability Act of 1996

HIPAA Security Rule

Centers for Medicare and Medicaid Services

Department of Health and Human Services

<http://www.cms.gov/HIPAAGenInfo/>

Medical Privacy–National Standards to Protect the Privacy of Personal Health Information

Office for Civil Rights–HIPAA

Office for Civil Rights

Department of Health and Human Services

<http://www.hhs.gov/ocr/hipaa/>

Human Subjects Regulations

Application for, and exemption from, IRB approval

Office for Human Research Protections

Department of Health and Human Services

<http://www.hhs.gov/ohrp/policy/hsdc95-02.html>

Frequently asked questions

Office for Human Research Protections

Department of Health and Human Services

<http://answers.hhs.gov/ohrp/>

⁸ All listed Web sites were accessed on January 7, 2016.

Genetic Information Nondiscrimination Act of 2008

<http://thomas.loc.gov/cgi-bin/bdquery/z?d110:h.r.00493:>

Genetic Nondiscrimination Fact Sheet

<http://www.genome.gov/10002328>

Guidance on the Genetic Information Nondiscrimination Act: Implications for Investigators and Institutional Review Boards

<http://www.hhs.gov/ohrp/policy/gina.pdf>

Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens That Are Not Individually Identifiable

Food and Drug Administration

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm078384.htm>

Guidance on Research Involving Coded Private Information or Biological Specimens

Office for Human Research Protections

Department of Health and Human Services

<http://www.hhs.gov/ohrp/policy/cdebiol.html>

Human Subjects Policy Guidance

Office for Human Research Protections

Department of Health and Human Services

<http://www.hhs.gov/ohrp/policy/index.html#human>

Office for Human Research Protections

Department of Health and Human Services

<http://www.hhs.gov/ohrp/>

Informed Consent Policy Guidance

Issues to Consider in the Research Use of Stored Data or Tissues

Office for Human Research Protections

Department of Health and Human Services

<http://www.hhs.gov/ohrp/policy/reposit.html>

Office for Human Research Protections

Department of Health and Human Services

<http://www.hhs.gov/ohrp/policy/index.html#informed>

Policies for responding to requests for discontinuation of participation in research

Office for Human Research Protections

Department of Health and Human Services

<http://www.hhs.gov/ohrp/policy/subjectwithdrawal.pdf>

<http://edocket.access.gpo.gov/2008/pdf/E8-28387.pdf>

Informatics System Security

Risk Management Guide for Information Technology Systems

National Institute of Standards and Technology

<http://csrc.nist.gov/publications/PubsSPs.html#800-30>

Laboratory Practices

Clinical Laboratory Improvement Amendment (CDC web site)

<http://wwwn.cdc.gov/clia/>

Good Laboratory Practices <http://www.oecd.org/chemicalsafety/testing/goodlaboratorypracticeglp.htm>

International Organization for Standardization (ISO9000)

<http://www.iso.org/iso/home.htm>

ISBER

<http://www.isber.org>

U.S. Food and Drug Administration (FDA) Quality System Regulation, 21 CFR 820

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=820>

National Cancer Institute

Biorepositories and Biospecimen Research Branch

<http://biospecimens.cancer.gov/>

Biospecimen Research Network

<http://biospecimens.cancer.gov/researchnetwork/>

[Biospecimen Research Database](#)

<https://brd.nci.nih.gov/brd/>

[Biobank Economic Modeling Tool](#)

<http://biospecimens.cancer.gov/resources/bemt.asp>

NCI Best Practices Frequently Asked Questions

<http://biospecimens.cancer.gov/practices/faq.asp>

Specimen Resource Locator

<http://biospecimens.cancer.gov/locator>

Symposium-Workshop on [Custodianship and Ownership Issues in Biospecimen Research](#)

<http://biospecimens.cancer.gov/resources/publications/workshop/cow.asp>

National Institutes of Health Policies and Guidelines

Certificates of Confidentiality Kiosk

Office of Extramural Research

National Institutes of Health

<http://grants2.nih.gov/grants/policy/coc/index.htm>

Conflict of Interest

Office of Extramural Research

National Institutes of Health

<http://grants.nih.gov/grants/policy/coi/>

Guidelines for Research Involving Recombinant DNA Molecules

Office of Biotechnology Activities

National Institutes of Health

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-052.html>

NIH Data Sharing Policy
Office of Extramural Research
National Institutes of Health
http://grants.nih.gov/grants/policy/data_sharing/

[NIH Genomic Data Sharing Policy](#)

<https://gds.nih.gov/03policy2.html>

NIH Research Tools Policy
Sharing Biomedical Research Resources: Principles and Guidelines for Recipients of NIH Research Grants and Contracts
Office of Technology Transfer
National Institutes of Health
<http://www.gpo.gov/fdsys/pkg/FR-1999-12-23/pdf/99-33292.pdf>

Other Biospecimen Resource References

Case Studies of Existing Human Tissue Repositories—“Best Practices” for a Biospecimen Resource for the Genomic and Proteomic Era
<http://www.rand.org/pubs/monographs/MG120/index.html>

Handbook of Human Tissue Sources—A National Resource of Human Tissue Samples
http://www.rand.org/pubs/monograph_reports/MR954/

Standardized Systems for Clinical and Pathology Data

American Joint Committee on Cancer TNM Staging
<https://cancerstaging.org/references-tools/Pages/What-is-Cancer-Staging.aspx>
(close any pop-up box indicating sign-on is necessary)

Cancer Care Ontario Program in Evidence-Based Care
<https://www.cancercare.on.ca/about/programs/pebc/>

College of American Pathologists Cancer Protocols and Checklists
<http://tinyurl.com/CAPProtocols>

International Classification of Diseases
<http://www.who.int/classifications/icd/en/>

International Classification of Diseases for Oncology
<http://www.who.int/classifications/icd/adaptations/oncology/en/index.html>

National Comprehensive Cancer Network Guidelines and Clinical Resources
http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

North American Association of Central Cancer Registries Data Standards and Data Dictionary
<http://www.naaccr.org/LinkClick.aspx?fileticket=H7hn-uneaGc%3D&tabid=133&mid=473>

Systematized Nomenclature of Medicine—Clinical Terms[®] (SNOMED CT)

http://www.nlm.nih.gov/research/umls/Snomed/snomed_main.html

Glossary of Terms

This glossary is included to provide instruction as to how terms used in the *NCI Best Practices for Biospecimen Resources* should be interpreted. Wherever possible, standardized definitions from Federal documents and/or the NCI Thesaurus were used.⁹ Where such sources were not available or appropriate, definitions were selected from widely used texts, such as *Black's Law Dictionary* (8th ed.), *Taber's Cyclopedic Medical Dictionary* (20th ed.), Merriam-Webster's Online Dictionary; reports specific to biospecimen resources, such as *ISBER Best Practices for Repositories, Third Edition* (2012), and RAND Corporation's *Case Studies of Existing Human Tissue Repositories* (2003); or relevant Web sites such as the CDC Web site. The citation "*NCI Best Practices* working definition" refers to definitions drafted specifically for this document by the NCI in consultation with appropriate experts. In some cases, two definitions may be listed for a single term to convey both a general and a biospecimen resource-specific meaning or to provide definitions from two Federal regulations. Where two definitions are listed, the first definition contains the meaning most relevant to the *NCI Best Practices*.

Access. The right to obtain or make use of or take advantage of something (as services or membership); the right to enter (NCI Thesaurus).

Aerosol. A fine mist or spray that contains minute particles (Centers for Disease Control and Prevention Special Pathogens Branch, Glossary of Terms, http://hickmancharterscioly.pbworks.com/f/Glossary+_CDC+Special+Pathogens+Branch.pdf).

Age of majority. The age—usually 18 or 21 years—at which a person achieves full legal rights to make one's own decisions, enter into contracts, and be held personally accountable for the consequences of one's actions (Taber's Medical Dictionary).

Aliquot. 1. Pertaining to a portion of the whole; any one of two or more samples of something, of the same volume or weight (NCI Thesaurus). 2. A process wherein a biospecimen is divided into separate parts which are typically stored in separate containers as individual samples (ISBER 2008).

Analyte. A substance or chemical constituent that is determined in an analytical procedure (ISBER 2008).

Annotation. Explanatory information associated with a biospecimen (*NCI Best Practices* working definition).

Assay. A qualitative or quantitative analysis performed to determine the amount of a particular constituent in a biospecimen (adapted from NCI Thesaurus).

Associated data. Any factual information affiliated with a biospecimen, including but not limited to research, phenotypic, clinical, epidemiologic, and biospecimen-resource procedural data (*NCI Best Practices* working definition).

Audit. 1. A documented review of procedures, records, personnel functions, equipment materials, facilities, and/or vendors to evaluate adherence to written standard operating procedures or government laws and regulations (ISBER 2008). 2. To perform an audit (Merriam-Webster's Online Dictionary).

Barcode. A machine-readable representation of information in a visual format on a surface (NCI Thesaurus).

⁹ A collaborative effort of the NCI Office of Communications and the NCI Center for Bioinformatics to standardize terminology within the NCI, available at <http://ncit.nci.nih.gov/>.

Best practice. A technique, process, or protocol that has been shown or is otherwise believed to be state-of-the-science in that it provides superior results to those achieved by any other technique, process, or protocol. Best practices may evolve as new evidence emerges. While best practices are consistent with all applicable ethical, legal, and policy statutes, regulations, and guidelines, they differ from guidance, policy, or law in that they are recommendations and are neither enforced nor required (*NCI Best Practices* working definition).

Biohazard. A biological or chemical substance that exerts toxic or pathologic effects on living entities (NCI Thesaurus).

Biomarker. A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition. Also called molecular marker and signature molecule (NCI Online Cancer Dictionary).

Biomolecule. An organic molecule and especially a macromolecule (as a protein or nucleic acid) in living organisms (Merriam-Webster's Online Dictionary).

Biorepository. An organization, place, room, or container (a physical entity) where biospecimens are stored. In the context of the *NCI Best Practices*, only biorepositories containing human specimens intended for research purposes (research biorepositories) are addressed. The physical structure, policies, biospecimens, and data contained within it are defined collectively as a biospecimen resource, defined below (*NCI Best Practices* working definition).

Biosafety. Safety with respect to the effects of biological research on humans and the environment (Merriam-Webster's Online Dictionary).

Biosafety level. Specific combinations of work practices, safety equipment, and facilities, which are designed to minimize the exposure of workers and the environment to infectious agents. Biosafety level 1 applies to agents that do not ordinarily cause human disease. Biosafety level 2 is appropriate for agents that can cause human disease, but whose potential for transmission is limited. Biosafety level 3 applies to agents that may be transmitted by the respiratory route which can cause serious infection. Biosafety level 4 is used for the diagnosis of exotic agents that pose a high risk of life-threatening disease, which may be transmitted by the aerosol route and for which there is no vaccine or therapy (Centers for Disease Control and Prevention Special Pathogens Branch, Glossary of Terms,

http://hickmancharterscioly.pbworks.com/f/Glossary+_CDC+Special+Pathogens+Branch.pdf

Biospecimen. A quantity of tissue, blood, urine, or other human-derived material. A single biopsy may generate several biospecimens, including multiple paraffin blocks or frozen biospecimens. A biospecimen can comprise subcellular structures, cells, tissue (e.g., bone, muscle, connective tissue, and skin), organs (e.g., liver, bladder, heart, and kidney), blood, gametes (sperm and ova), embryos, fetal tissue, and waste (urine, feces, sweat, hair and nail clippings, shed epithelial cells, and placenta). Portions or aliquots of a biospecimen are referred to as samples (*NCI Best Practices* working definition).

Biospecimen resource. A collection of human specimens and associated data for research purposes, the physical entity in which the collection is stored, and all associated processes and policies. Biospecimen resources vary considerably, ranging from formal institutions to informal collections in a researcher's freezer (*NCI Best Practices* working definition).

Biospecimen resource governance. The set of authorities, processes, and procedures guiding key operational decisions made within the resource. Governance affects access to biospecimens as well as custodial relationships and responsibilities and should be part of the resource's general custodianship plan (*NCI Best Practices* working definition).

Biospecimen resource informatics system. The software, hardware, documentation, support, operating procedures, and training necessary to annotate, track, and distribute biospecimens within a biospecimen resource or resources (*NCI Best Practices* working definition).

Bloodborne pathogen. Pathogenic microorganisms that are present in human blood and can cause disease in humans. These pathogens include, but are not limited to, hepatitis B virus and human immunodeficiency virus (Occupational Safety and Health Administration Bloodborne Pathogen Standards, [29 CFR § 1910.1030](#)).

Certificate of Confidentiality. Issued by the National Institutes of Health (NIH) to protect identifiable research information from forced disclosure. It allows the Investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the Federal, State, or local level. Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation (Certificates of Confidentiality Kiosk Web site, <http://grants.nih.gov/grants/policy/coc/>).

Clinical data. 1. Factual information (as measurements or statistics) or observations relating to the patient used as a basis for reasoning, discussion, or calculation pertaining to clinical trials, diagnosis, or treatment (*NCI Best Practices* working definition). 2. Data obtained through patient examination or treatment (NCI Thesaurus).

Clinical research. Research conducted with human subjects or on material of human origin in which an investigator directly interacts with human subjects; includes development of new technologies, study of mechanisms of human diseases, therapy, clinical trials, epidemiology, behavior and health services research (NCI Thesaurus).

Code of Federal Regulations (CFR). The annual collection of executive-agency regulations published in the daily *Federal Register*, combined with previously issued regulations that are still in effect (Black's Law Dictionary). See <http://www.gpo.gov/fdsys/browse/collectionCfr.action?collectionCode=CFR> for more information.

Coded. Having (1) identifying information (such as name or Social Security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or biospecimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and (2) a key to decipher the code, enabling linkage of the identifying information to the private information or biospecimens (Office for Human Research Protections, Guidance on Research Involving Coded Private Information or Biological Specimens, <http://www.hhs.gov/ohrp/policy/cdebiol.html>).

Common data elements. Annotations collected in a uniform manner across multiple institutions to allow sharing of data in a standardized format (BBRB Glossary, <http://biospecimens.cancer.gov/patientcorner/glossary.asp>).

Confidentiality. Treatment of information so that it is not divulged in ways that are inconsistent with the understanding of the original disclosure. Particularly, the ethical principle or legal right that a physician or other health professional will hold secret all information relating to a patient, unless the patient gives consent permitting disclosure (NCI Thesaurus).

Conflict of interest. 1. Exists when the designated official(s) reasonably determines that a Significant Financial Interest could directly and significantly affect the design, conduct, or reporting of the Public Health Service–funded research. Examples of conditions or restrictions that might be imposed to manage conflicts of interest include, but are not limited to: (1) Public disclosure of significant financial interests; (2) Monitoring of research by independent reviewers; (3) Modification of the research plan; (4) Disqualification from participation in all or a portion of the research funded by the Public Health Service; (5) Divestiture of significant financial interests; or (6) Severance of relationships that create actual or potential conflicts ([42 CFR § 50.605](#)).

<http://www.gpo.gov/fdsys/pkg/CFR-2013-title42-vol1/pdf/CFR-2013-title42-vol1-sec50-605.pdf>). 2. Prejudice or bias that may occur when one's impartiality is compromised by opportunities for personal gain or occupational advancement, or by the chance that one's work may support a favored point of view or social agenda (Taber's Medical Dictionary).

Consumables (a.k.a. disposables). Items that are liable to be used up or exhausted (*NCI Best Practices* working definition).

Cost recovery. Charging a sufficient amount for products and services such as biospecimen collection, processing, storage, and shipping to recover or partially recover operational fees incurred by a biospecimen resource (*NCI Best Practices* working definition).

Custodianship. The caretaking responsibility for biospecimens that extends from collection through research use. Responsible custodianship requires careful planning and transparent policies to ensure the long-term physical quality of the biospecimens, the privacy of human research participants, the confidentiality of associated data, and the appropriate use of biospecimens and data (*NCI Best Practices* working definition).

Data. A collection or single item of factual information, derived from measurement or research, from which conclusions may be drawn (NCI Thesaurus).

Demographic data. Information pertaining to the statistical characterization of human populations or segments of human populations; e.g., characterization by age, sex, race, or income (adapted from NCI Thesaurus).

Deviation. An intentional or unintentional event that is a departure from a procedure or a normal practice (ISBER 2008).

Discontinuation of participation. Discontinuation of a subject's participation in research means discontinuation of one or more of the following activities described in the IRB-approved protocol: (1) interacting or intervening with the subject; (2) collecting individually identifiable private information about the subject without the investigator interacting or intervening with the subject; (3) collecting individually identifiable biological specimens originating from the subject without the investigator interacting or intervening with the subject; or (4) using or testing individually identifiable biological specimens already collected by the Investigator (Office for Human Research Protections, Guidance on Important Considerations for When Participation of Human Subjects in Research Is Discontinued, <https://www.federalregister.gov/articles/2010/09/21/2010-23517/guidance-on-withdrawal-of-subjects-from-research-data-retention-and-other-related-issues>).

Disposition. Final destination of biospecimens (ISBER 2008).

Distribution. A process that includes receipt of request for samples, selection of appropriate samples, and final inspection, in conjunction with subsequent shipment and delivery of samples to another biospecimen resource, biospecimen collection center, or laboratory (*NCI Best Practices* working definition).

End user. 1. A health care practitioner, scientist, or laboratory staff member who performs an appropriate procedure, test, or archival function (ISBER 2008). 2. The ultimate consumer of a finished product (Merriam-Webster's Online Dictionary).

Epidemiologic. Of or relating to epidemiology, the study of the causes, incidence, and distribution of disease in the population and its application for prevention or control (NCI Thesaurus).

Evaluation. Systematic, objective appraisal of the significance, effectiveness, and impact of activities or condition according to specified objectives and criteria (NCI Thesaurus).

Extramural. External to the National Institutes of Health (*NCI Best Practices* working definition).

Genomics. The study of the complete genetic complement of an organism or organ (Taber’s Medical Dictionary).

Honest broker. An individual, organization, or system acting for, or on behalf of, a covered entity to collect and provide health information to research investigators in such a manner whereby it would not be reasonably possible for the investigators or others to identify the corresponding patients-subjects directly or indirectly. The honest broker cannot be one of the investigators. The information provided to the investigators by the honest broker may incorporate linkage codes to permit information collation and/or subsequent inquiries (i.e., a “re-identification code”); however, the information linking this reidentification code to the patient’s identity must be retained by the honest broker and subsequent inquiries are conducted through the honest broker (NCI Thesaurus).

Human research participant. See Human subject.

Human subject. A living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual or (2) identifiable private information ([45 CFR § 46.102\(f\)](#)).

Identifiable. The identity of the subject is or may readily be ascertained by the investigator or associated with the information ([45 CFR § 46.102\(f\)](#)).

Informatics. An occupational discipline which unites information science with computer science. It is concerned with the development of techniques for the collection and manipulation of data, and the use of such data (NCI Thesaurus).

Informed consent. A decision to participate in research, taken by a competent individual who has received the necessary information; who has adequately understood the information; and who, after considering the information, has arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation (Council for International Organizations of Medical Sciences [CIOMS]. International Ethical Guidelines for Biomedical Research Involving Human Subjects. “Guideline 4: Individual Informed Consent” [2002]).

Infrastructure. The basic facilities, equipment, or underlying framework that are necessary for a system or organization to function (NCI Thesaurus).

Institutional review board (IRB). A specially constituted review body established or designated by an entity to protect the rights and welfare of human subjects recruited to participate in biomedical or behavioral research. The relevant regulatory requirements for an IRB are provided at <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.107> and [21 CFR 56](#) (Trans-NIH Bioethics Committee Framework Guidelines).

Intellectual property. A commercially valuable product of the human intellect, in a concrete or abstract form, such as a copyrightable work, a protectable trademark, a patentable invention or a trade secret (Black’s Law Dictionary).

Interoperability. The ability of systems or tools to both access and use data from a remote data resource (BBRB Glossary, <http://biospecimens.cancer.gov/patientcorner/glossary.asp>).

Invention. Any art or process (way of doing or making things), machine, manufacture, design, or composition of matter, or any new and useful improvement thereof, or any variety of plant, which is or may be patentable

under the patent laws of the United States (U.S. Patent and Trademark Office, Glossary of Terms, <http://www.uspto.gov/main/glossary/index.html#i>).

Inventory. 1. A detailed, itemized list, report, or record of samples in a biospecimen resource, especially a periodic survey of all stored biospecimens (*NCI Best Practices* working definition). 2. The act or process of taking an inventory (Merriam-Webster's Online Dictionary).

Label. Any written, printed, or graphic material on or affixed to a biospecimen container or package (ISBER 2008).

Longitudinal data. Data in which the same units are observed over multiple time periods (U.S. Department of Labor, Bureau of Labor Statistics, Glossary, <http://www.bls.gov/bls/glossary.htm#L>

Material transfer agreement. An agreement that governs the transfer of tangible research materials and data between two organizations, when the recipient intends to use it for his or her own research purposes. It defines the rights and obligations of the provider and the recipient with respect to the use of the materials (ISBER 2008).

Package. A product container with any accompanying materials or components (NCI Thesaurus).

Paraffin embedded. A method of preserving biospecimens where they are chemically or otherwise fixed and then infiltrated with molten wax, which later solidifies (*NCI Best Practices* working definition).

Patent. A property right granted by the U.S. Government to an inventor "to exclude others from making, using, offering for sale, or selling the invention throughout the United States or importing the invention into the United States" for a limited time in exchange for public disclosure of the invention when the patent is granted (U.S. Patent and Trademark Office, Glossary of Terms, <http://www.uspto.gov/main/glossary/index.html#p>).

Preservation. Use of chemical agents, alterations in environmental conditions, or other means during processing to prevent or retard biological or physical deterioration of a biospecimen (ISBER 2008).

Prevalence. The total number of cases of a given disease in a specified population at a designated time. It is differentiated from "incidence," which refers to the number of new cases in the population at a given time (NCI Thesaurus).

Privacy. 1. The condition or state of being free from public attention to intrusion into or interference with one's acts or decisions (Black's Law Dictionary). 2. The ability of a person to control the availability of information about and exposure of him- or herself (adapted from NCI Thesaurus).

Private information. Information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record) ([45 CFR § 46.102\(f\)](#)).

Procedure. A series of steps designed to result in a specific outcome when followed in order (ISBER 2008).

Process validation studies. The process of demonstrating that a specific procedure will consistently produce expected results within predetermined specifications (ISBER 2008).

Processing. Any procedure employed after biospecimen collection but prior to its distribution, including preparation, testing, and releasing the biospecimen to inventory and labeling (ISBER 2008).

Project management. The application of knowledge, skills, tools and techniques to a broad range of activities to meet the requirements of the particular project **Proteomics.** The global analysis of cellular proteins.

Proteomics uses a combination of sophisticated techniques including two-dimensional (2D) gel electrophoresis, image analysis, mass spectrometry, amino acid sequencing, and bio-informatics to resolve comprehensively, to quantify, and to characterize proteins. The application of proteomics provides major opportunities to elucidate disease mechanisms and to identify new diagnostic markers and therapeutic targets (NCI Thesaurus).

Quality. Conformance of a biospecimen or process with pre-established specifications or standards (ISBER 2008).

Quality assurance. An integrated system of management activities involving planning, implementation, documentation, assessment, and improvement to ensure that a process or item is of the type and quality needed for the project. Same as quality management system (ISBER 2008).

Quality control. Specific tests defined by the QA or QMS Program to be performed to monitor procurement, processing, preservation and storage; biospecimen quality; and test accuracy. These may include but are not limited to performance evaluations, testing, and controls used to determine accuracy and reliability of the biospecimen resource's equipment and operational procedures as well as monitoring of the supplies, reagents, equipment, and facilities (ISBER 2008).

Quality management system. See Quality assurance.

Reach-through rights. Rights claimed by the provider of materials to the recipient's downstream discoveries to which the provider would not otherwise be entitled through its ownership or patent coverage of the material alone. Examples of reach-through rights required by providers in exchange for use of their material by the recipient might include ownership of recipient's discoveries, license exclusivity, or payments upon the sale of the discovery. Reach-through rights may give the provider an unfairly high level of compensation for the research use of the material by the recipient (*NCI Best Practices* working definition).

Research. 1. Systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge ([CFR 45 § 46.102\(d\)](#)). 2. Systematic investigation into a subject in order to discover facts, establish or revise a theory, or develop a plan of action based on the facts discovered (NCI Thesaurus).

Resource sharing. The sharing of materials and data in a timely manner (NCI Thesaurus).

Retrieval. The removal, acquisition, recovery, harvesting, or collection of biospecimens (ISBER 2008).

Sample. 1. A portion of a biospecimen (*NCI Best Practices* working definition). 2. A single unit containing material derived from one biospecimen (ISBER 2008). 3. Serving as an illustration or example (Merriam-Webster's Online Dictionary).

Secondary research. Any research use beyond the scope of the primary study. See Primary research (*NCI Best Practices* working definition).

Simple letter agreement (SLA). Streamlined form of material transfer agreement approved for use at the NIH. The NIH encourages the use of the SLA to facilitate exchanges between academic institutions (NCI Technology Transfer Branch, <https://ttc.nci.nih.gov/forms/mta.php> and <http://ttc.nci.nih.gov/>).

Space planning. The process of designing the layout of a building, suite, or laboratory for optimal efficiency in the intended purpose (*NCI Best Practices* working definition).

Specimen. See Biospecimen.

Stakeholder. One that has a stake or an interest in an enterprise. In the context of the *NCI Best Practices*, the term stakeholder embraces research participants, patient advocates, researchers, clinicians, and biospecimen resource operational/managerial personnel (*NCI Best Practices* working definition).

Standard operating procedure. An established procedure to be followed in carrying out a given operation or in a given situation (NCI Thesaurus).

Standard operating procedures (SOPs) manual. A group of SOPs detailing specific policies of a repository and the procedures required to be used by the staff/personnel (ISBER 2008).

Standard precautions. The CDC publication titled “Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings 2007” is also known as “Standard Precautions.” Standard precautions are based on the principle that all blood, body fluids, secretions, excretions except sweat, nonintact skin, and mucous membranes may contain transmissible infectious agents, and include a group of infection-prevention practices. These include: hand hygiene; use of gloves, gown, mask, eye protection, or face shield, depending on the anticipated exposure; and safe injection practices. Also, equipment or items in the patient environment likely to have been contaminated with infectious body fluids must be handled in a manner to prevent transmission of infectious agents (“Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings 2007,” <http://www.cdc.gov/hicpac/pdf/isolation/Isolation2007.pdf>).

Storage. 1. Maintenance of biospecimens under specified conditions for future use (ISBER 2008).

Sustainable. Of, relating to, or being a method of using a resource so that the resource is not depleted (adapted from Merriam-Webster’s Online Dictionary).

Tissue. An aggregate of cells with different specialized characteristics that are organized anatomically, usually in the fixed framework of an organic matrix. The architectural organization that is maintained contributes to the performance of a specific collective function. Tissues are parts of organs. The term tissue is most often referred to in the context of solid tissue, as originating from a solid organ; however, tissue also can be defined broadly to include collections of cells and the extracellular matrix and/or intercellular substances from bodily fluids such as blood (*NCI Best Practices* working definition).

Uniform Biological Material Transfer Agreement (UBMTA). A Master Agreement among the NIH, universities, and other nonprofit research facilities used to expedite transfer of research materials among noncommercial entities (NCI Technology Transfer Branch, <https://ttc.nci.nih.gov/forms/mta.php>). More information about the terms of the UBMTA and its signatories is available at (<http://www.bioinfo.com/ubmta.html>).

Unique identifier. A set of characters used as a code that is unique in the context or the system for which it is created. It serves as a means of identification and reference (often instead of a name) for an entity, person, thing, function, procedure, activity, variable, or body of data (NCI Thesaurus).

Use case. A document that describes the interaction between a user (or other initiator of the interaction) and a system, represented as a sequence of simple steps leading to a particular goal (NCI Thesaurus).

Validation (of procedures or equipment). 1. The act of confirming a product or service meets the requirements for which it was intended (Babylon Business Dictionary). 2. A statistical method of partitioning a sample of data into subsets such that the analysis is initially performed on a single subset, while the other subsets are retained for subsequent use in confirming and validating the initial analysis (NCI Thesaurus).

Acronym List

BMBL	Biosafety in Microbiological and Biomedical Laboratories
BSL	biosafety level
BBRB	NCI Biorepositories and Biospecimen Research Branch
CAP	College of American Pathologists (BAP: CAP Biorepository Accreditation Program)
CDC	Centers for Disease Control and Prevention
CDE	common data element
CMMI	Capability Maturity Model Integration
CMS	Center for Medicaid and Medicare Services
COI	conflict of interest
DHHS	U.S. Department of Health and Human Services
DNA	deoxyribonucleic acid
FDA	U.S. Food and Drug Administration
GINA	Genetic Information Nondiscrimination Act
HIPAA	Health Insurance Portability and Accountability Act
HITECH	Health Information Technology for Economic and Clinical Health
IATA	International Air Transport Association
IP	intellectual property
IRB	institutional review board
MTA	material transfer agreement
NCI	National Cancer Institute
NHGRI	National Human Genome Research Institute
NIST	National Institute of Standards and Technology
OHRP	Office for Human Research Protections
OSHA	Occupational Safety and Health Administration
PHI	protected health information
PHS	Public Health Service
QA/QC	quality assurance/quality control
QMS	quality management system
RNA	ribonucleic acid
SOP	standard operating procedure

Appendices

Appendix 1. Minimal Clinical Data Set

The Minimal Clinical Data Set in this appendix is the minimal clinical data that are recommended for annotation of disease state or risk of cancer in biospecimen resources. The items in this recommended data set are not meant to be inclusive and are only suggested examples. Different biospecimen resources may require more or less detailed annotations that focus on the primary use of the clinical biospecimens. Good practice suggests that the data set for clinical annotation be tailored to the needs of the users of the biospecimen resource. Also this Minimal Clinical Data Set is not to be confused with other data sets such as that used by CMS to evaluate nursing home patients (<http://www.cms.hhs.gov/MDSPubQIandResRep/>).

Item		Notes
Age		or ≥ 90, at collection
Exposures (where age > 18)	Smoking	
	Drinking	
	Occupation	
Gender		
Race		
Ethnicity		
Disease diagnosis/Normal		
Source/Method of diagnosis		
Treatment type/None		
Height		
Weight		
Family history of cancer		
For tissue biospecimens only,	Histologic type	Also record for blood biospecimens in bloodborne cancers
	Grade	
	Size	
	Nodal status (pos/neg, # pos/total nodes, etc.)	
	Pathologic TNM status	
	Pathologic TNM stage	
	Procedure	Procedure by which biospecimen was obtained
Biomarkers		Biomarkers used in routine care; e.g. Estrogen and Progesterone receptor sensitivity
Outcome—or will it be possible to get these data when outcome is known	Death	Year only
	Date of last cancer follow-up	Year only

	Recurrence (local, distant, unknown)	
Collection method		
Comorbidity		

Appendix 2. Additional Resources Related to Ethical, Legal, and Policy Issues in Biospecimen Research

The resources listed below are not intended to be exhaustive but rather to provide useful examples and references for biospecimen resources. All Web links were last accessed on August 30, 2011.

I. General Resources Related to Ethical, Legal, and Policy Issues in Biospecimen Research

The reports and resources listed below provide an overview of ethical, legal, and policy challenges in biospecimen research. Topics include State and international regulations related to biospecimens and tools for institutional review boards (IRBs) and biospecimen resource managers.

A. NCI Documents

NCI Brochure: Donating Your Blood, Tissue and Other Samples

<http://biospecimens.cancer.gov/global/pdfs/MedicalResearchPatientBrochure-508.pdf>

NCI ELSI Workshop Summaries:

(1) NCI Think Tank on Identifiability of Biospecimens and 'Omic Data

<http://epi.grants.cancer.gov/events/identifiability/#summary>

(2) Workshop on Release of Research Results to Participants in Biospecimen Studies

<http://biospecimens.cancer.gov/resources/publications/workshop/rrra.asp>

(3) Workshop on Ethical Use of Pediatric Biospecimens in Research

<http://biospecimens.cancer.gov/resources/publications/workshop/eupbr.asp>

(4) Workshop on Custodianship and Ownership in Biospecimen Research

<http://biospecimens.cancer.gov/global/pdfs/CaOSumm.pdf>

(5) International Symposium to Harmonize Biorepository Practices

http://biospecimens.cancer.gov/global/pdfs/Barker20051110_summary.pdf

B. Documents from Other Sources

The President's Commission for the Study of Bioethical Issues <http://www.bioethics.gov/> recently published two key reports impacting research involving biospecimens and biospecimen resources. The first (October 2012) examines the use of biospecimens to conduct whole genome sequencing, including considerations on informed consent, privacy and data sharing:

http://bioethics.gov/sites/default/files/PrivacyProgress508_1.pdf. The second:

<http://bioethics.gov/node/3186> (December 2013) explores the ethical issues surrounding the return of incidental findings in research involving biospecimens.

The Secretary's Advisory Committee on Human Research Protection (SACHRP) developed a document addressing a number of practical and regulatory issues about the collection, storage, distribution, and future research use of biospecimens and associated data. These issues were deliberated over the course of

several SACHRP meetings in 2009-2010. The final recommendations take the form of a series of “Frequently Asked Questions, each presented as a commonly-encountered scenario and a suggested response addressing both regulatory and ethical human subject concerns. The goal was to provide a framework for IRBs, institutions and investigators to consider individual research scenarios without prescribing specified outcomes, recognizing that each decision will always be fact-specific. The recommendations can be found on NCI’s website at

http://www.cancerdiagnosis.nci.nih.gov/resources/elsi/secretarys_advisory_committee.htm

Public Responsibility in Medicine & Research (PRIM&R) Human Tissue/Specimen Banking White Paper
The PRIM&R White Paper includes a discussion of the challenges and recommendations to the Federal regulatory and funding agencies as well as tools for IRBs, repository managers, and researchers in the form of educational materials, discussions of relevant issues, and points to consider.

<http://www.primr.org/Subpage.aspx?id=1929>

Research Involving Human Biological Materials: Ethical Issues and Policy Guidance—Volume I: Report and Recommendations of the National Bioethics Advisory Commission

This 1999 report from the National Bioethics Advisory Commission (NBAC) addresses the question of whether the Common Rule is effective in protecting human subjects from harm in research involving biospecimens. The NBAC report also provides recommendations related to biospecimen research, including interpretations of several key terms and concepts in the Common Rule.

<https://bioethicsarchive.georgetown.edu/nbac/pubs.html>

International Compilation of Human Research Protections

This compilation was developed by the Office for Human Research Protections (OHRP) for IRBs/ethics committees, researchers, sponsors, and others who are involved in international research. The report includes a table for each country that lists the key organizations, legislation, regulations, and guidelines related to human biological materials.

<http://www.hhs.gov/ohrp/international/>

II. Sample Informed Consent Documents

The following list of sample informed consent documents is provided to guide and inform biospecimen resources about possible approaches to the informed consent process. These documents may be adapted depending on the nature of the resource and its mission.

A. NCI Documents

The Cancer Genome Atlas (TCGA)

The NCI and the National Human Genome Research Institute have developed informed consent documents that are consistent with the goals and activities of TCGA, a comprehensive and coordinated effort to accelerate the understanding of the molecular basis of cancer through the application of genome analysis technologies. Both documents, one for retrospective biospecimen collections and another for prospective collections, specifically address genetic research, broad sharing of biospecimens and clinical data, the possibility of future research use, the deposition of genomics data into electronic database with partial public access, and the risk of loss of privacy.

<http://cancergenome.nih.gov/abouttcga/policies/informedconsent>

The Genotype-Tissue Expression (GTEx) Project

The NCI and National Human Genome Research Institute have developed an informed consent document for the Genotype-Tissue Expression (GTEx) project. GTEx is a NIH Common Fund project that is collecting biospecimens and clinical data from 900 non-diseased postmortem donors. This document provides a sample for obtaining assent from next-of-kin or a family decision maker to obtain and use these tissues for genomic and other research endeavors.

Add link to sample GTEx informed consent document

B. *Documents from Other Sources*

Public Project in Population Genetics (P3G)

P3G designed an informed consent template for use in prospective, longitudinal population genomics studies based on approaches used by P3G members.

General information:

<http://p3g.org/resources>

Sample consent form:

http://p3g.org/system/files/biobank_toolkit_documents/P3G%20Generic%20Info%20Pamphlet%20and%20OConsent%20Form%20for%20Biobanks_0.pdf

Biobank tool kit:

<http://p3g.org/resources/biobank-toolkit>

III. Patient Information Documents

The following list of sample patient information documents is provided to guide and inform biospecimen resources about additional resources that may be useful during the informed consent process. These documents are intended to explain the informed consent process and/or the importance of biospecimens in research to a general audience and may be adapted depending on the nature and mission of the resource.

A. *NCI Documents*

Guide to Understanding Informed Consent

This guide explains what a human research participant should expect during the informed consent process, explains the importance of the informed consent process to clinical human research participants, and describes how informed consent fits into a larger system that protects the welfare of people who take part in clinical trials.

<http://www.cancer.gov/clinicaltrials/learningabout/patientsafety/informedconsent>

Providing Your Tissue for Research

This six-page booklet is meant to complement the face-to-face education that occurs between clinicians and potential clinical trial participants. It provides a balanced discussion of questions and answers on how biospecimens are collected and used in research.

<http://biospecimens.cancer.gov/global/pdfs/ProvidingYourTissueforResearch.pdf>

B. *Documents from Other Sources*

Research Advocacy Network

The Research Advocacy Network (RAN) is a nonprofit organization working to bring together all participants in the medical research process. The RAN has developed booklets about the importance of biospecimens in research directed toward human research participants and IRB members. Documents are available in English or Spanish.

<http://www.researchadvocacy.org/>

IV. Resources for Simplifying Informed Consent Documents

Several groups have been established to provide recommendations on simplifying and improving the readability of informed consent documents. The following resources are not specific to biospecimen resources but instead provide general information on how to improve the informed consent process to meet the needs of human research participants.

A. *NCI Documents*

NCI Consent Template for Adult Cancer Trials (May 12, 2013):

The NCI, in conjunction with a working group of multidisciplinary experts, created a consent template for use in adult cancer trials. A web search for [NCI Consent Template for Adult Cancer Trials](#) will lead to the Word document.

FDA informed consent information sheet from 2014. This guideline on informed consent provides guidance for IRBs, clinical investigators, and sponsors.

<http://www.fda.gov/RegulatoryInformation/Guidances/ucm404975.htm>

B. *Documents from Others Sources*

Association of American Medical Colleges

The summary from a May 2007 strategic planning meeting titled “Universal Use of Short and Readable Informed Consent Documents: How Do We Get There?” includes a review of informed consent literature, potential approaches for improving informed consent, and success stories from the field.

<https://www.aamc.org/download/75282/data/hdicklermtgsumrpt53007.pdf>

This letter from AAMC provides feedback on the FDA guidance on informed consent.

<https://www.aamc.org/download/404310/data/aamccommentsonfdasdraftguidanceoninformedconsent.pdf>

Group Health Center for Health Studies

The Project to Review and Improve Study Materials (PRISM) is a Group Health Center for Health Studies initiative to improve the readability of print materials used in communication with study participants. The PRISM Readability Toolkit is a comprehensive resource that includes sample informed consent language, editing checklists, a reference guide for improving readability, and examples of how to improve readability.

<https://www.grouphealthresearch.org/about-us/capabilities/research-communications/prism/>

Appendix 3. Governance Plan

This governance plan is provided as an example to biospecimen resources to help with planning the resource and defining the authorities, processes, and procedures that are needed to guide key operational decisions. The governance plan should become part of the resource's documents and be available if requested. (Please see [Section C.1](#) of the *NCI Best Practices* for more information and additional recommendations related to custodianship.)

Principal Investigator:

Grant Number:

Project Title:

Project Period:

Name of the Biospecimen Resource (if different than the project):

A. *Name of the Custodian:*

B. *Summary of the Project:*

C. *Governance Structure of the Project (See [Section C.1.](#)):*

1. Outline the resource's management structure and discuss the roles and responsibilities of each management or oversight body.
2. Outline the resource's protocols and procedures that guide its operations and discuss whether the protocols are documented and approved by the institutional review board and/or a project oversight committee.

D. *Integrity of Biospecimens and Data (See Sections [C.1.5.](#) and [C.3.](#)):*

1. Describe the resource's protocols to ensure the physical integrity of collected biospecimens.
2. Describe the resource's protocols to ensure the integrity of the human research participants' data that accompany the biospecimens.

E. *Access to Biospecimens and Data (See Sections [C.3.](#) and [C.4.](#)):*

1. Outline the resource's protocols and procedures for the distribution of samples to investigators. Describe how the scientific merit, prioritization of access requests, and proposed research use are assessed and by what review group.
2. Describe whether samples will be accompanied by data and the type of data. Outline the safeguards that are in place to ensure that confidentiality of the data is not compromised.

F. *Release of Research Results (See Section [C.2.3.7.](#)):*

1. Outline the protocols that are in place for publication and dissemination of research results from biospecimen research. Describe the process for handling results that are potentially stigmatizing to groups.
2. Outline any process to provide educational materials to the public such as brochures, literature, meetings, or public Web sites.

G. *Legacy and Contingency Plans (See [Section C.1.2.](#)):*

1. Outline the resource's plans for the handling and disposition of biospecimens and associated data when reaching any of the following points: (a) End of the budget period of the grant, (b) loss of management or termination of funding, (c) accomplishment of the specific research objectives of the study, (d) depletion of biospecimens, or (e) achievement of critical data end points.

H. *Retention of Biospecimens, Data, and Records (See Sections [C.1.3.](#) and [C.2.3.1.](#)):*

1. Outline the resource's protocols for the handling and disposition of biospecimens and associated data sets following the discontinuation of participation by a human research participant.
2. Outline the resource's protocols for the retention of biospecimens, data, and records pertaining to informed consent and the identity of human research participants.

I. *Sharing of Resources* (See Sections [C.1.6.](#) and [C.5.](#)):

1. Outline the resource's protocols and procedures for the sharing of research data and tools generated from biospecimen research consistent with the NIH Data Sharing Policy (http://grants.nih.gov/grants/policy/data_sharing/) and the NIH Research Tools Policy (<https://www.ott.nih.gov/sites/default/files/documents/pdfs/Ferguson-AUTM-TTPM-3rd-ed-vol-4-Research-Tools.pdf>).
2. Outline the resource's protocols for communicating information to human research participants regarding the general type of research performed on biospecimens and the sharing of biospecimens with other researchers, when practicable.

J. *Conflict of Interests (COIs)* (See Sections [C.1.4.](#) and [C.6.](#)):

1. Describe the protocols for managing and limiting any potential COIs for the resource's staff consistent with [42 CFR Part 50 Subpart F](#), as well as applicable [NIH COI policies](#).

Appendix 4. Sample Material Transfer Agreement

The following Material Transfer Agreement (MTA) is intended to serve as a sample agreement for use between biospecimen resources and approved end-users receiving biospecimens and/or data. This sample MTA may need to be modified depending on the material and data that are being transferred and the specific requirements of the research project. Please note, this MTA is intended for transfer of deidentified biospecimens and data. (Please see [Section C.5](#) of the *NCI Best Practices* for more information and additional recommendations related to MTAs).

Sample Material Transfer Agreement For Transfers from Biospecimen Resources to Approved Third-Party End Users

This Material Transfer Agreement (the “Agreement”) is by and between <insert name of biospecimen resource> (“Provider”) and <insert name of third-party institution> (“Recipient”) regarding the transfer of human specimens, with or without associated data, from the <insert name of biospecimen resource> to approved third-party end users for research purposes as further defined below. Throughout this Agreement, Provider and Recipient are collectively referred to as the “Parties.” This Agreement will become effective upon the date of the last signature affixed below.

The Provider and Recipient agree as follows:

1. DEFINITIONS. Within this Agreement, the following terms will have the same meaning and effect as those used in the Standards for Privacy of Individually Identifiable Health Information set forth in 45 CFR Parts 160 and 164 (“HIPAA Privacy Rule”). These terms are repeated here for convenience:

(a) “De-identified” information is information that formerly contained individually identifiable health information but which has had all unique identifying information, numbers, characteristics, and codes removed such that the information a record contains cannot be used alone or in combination with other information to identify the individual who is the subject of the information (45 CFR 164.514). Identifying information includes, but is not limited to, the 18 categories of identifiers described in 45 CFR 164.514(b)(2).

(b) “Protected Health Information” or “PHI” means any information, whether oral or recorded in any form or medium: (i) that relates to the past, present, or future physical or mental condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual, and (ii) that identifies the individual or with respect to which there is a reasonable basis to believe the information can be used to identify the individual (45 CFR 164.103).

2. DESCRIPTION OF MATERIAL AND DATA. The Provider will transfer to the Recipient the following biospecimens and/or derivatives (“MATERIAL”): <insert description of specific samples to be transferred> with the following data (“DATA”): <insert description of specific data to be transferred, if applicable>.

3. COLLECTION OF MATERIAL AND DATA. The MATERIAL and DATA were collected and/or processed from human biospecimens as part of <insert name of biospecimen resource> in accordance with appropriate Federal and local laws, Assurances, and Institutional Review Board approvals related to human subjects research, as appropriate.

4. TRANSFER OF MATERIAL AND DATA. The MATERIAL and DATA provided by Provider will be de-identified and all Protected Health Information (PHI), as defined by the Federal Health Insurance Portability and Accountability Act (HIPAA, 45 C.F.R. 164) will have been removed.

5. RESPONSIBILITIES AND AUTHORIZATIONS OF RECIPIENT

(a) Recipient agrees to use the MATERIAL and DATA for the approved research project only (see [Appendix 1](#) “Research Project”) and will not use the MATERIAL and DATA for any unapproved commercial purposes, including selling or transferring to a third party for commercial purposes.

(b) Recipient is responsible for obtaining any necessary Human Subjects research approvals or exemptions required to use the MATERIAL and DATA at the respective institution. The MATERIAL and DATA will be used by the Recipient in compliance with all applicable Federal, state, and local statutes and regulations.

(c) Recipient will allow the use of MATERIAL and DATA only by <insert name of third party P.I.> (“Recipient Investigator”) and Recipient Investigator’s research team that are under the direct supervision of Recipient Investigator, and only after they have been informed of and agreed to the provisions and restrictions stated herein. Any transfer of MATERIAL and DATA to other than Recipient Investigator’s research team requires the advanced written approval of the Provider.

(d) It is acknowledged that the Recipient may already have in its possession or will obtain from another source, PHI related to the MATERIAL and DATA, and to which the Recipient may be subject to additional restrictions or

obligations under separate agreements. Recipient shall notify Provider in writing within five (5) working days of its discovery of any unauthorized use or disclosure of PHI related to the MATERIAL and DATA of which Recipient, its officers, employees, or agents become aware. Recipient shall take (i) prompt corrective action to cure any deficiencies or (ii) any action pertaining to such unauthorized disclosure required by applicable federal law.

(e) Recipient agrees to not identify or contact any donor, or living relative of a donor, who may have provided the MATERIAL or any DATA received by Recipient under this Agreement from Provider.

(f) Recipient agrees to report data, inventions, and publications resulting from the use of the MATERIAL and/or DATA to Provider.

6. THE MATERIAL AND DATA ARE NOT FOR USE IN HUMAN SUBJECTS OR FOR THE TREATMENT OR DIAGNOSIS OF HUMAN SUBJECTS.

7. DISCLAIMER. 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 HUMAN MATERIAL WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER PROPRIETARY RIGHTS. To the extent allowed by law, Recipient assumes liability for claims for damages against it by third parties which may arise from its use, storage, processing, distribution, or disposal of the MATERIAL except that, to the extent permitted by law, Provider shall be liable to Recipient when the damage is caused by the gross negligence or willful misconduct of Provider.

8. TERMINATION AND DISPOSAL. Either Party may terminate this Agreement with sixty (60) days written notice to the other Party. When the Research Project is completed or this Agreement is terminated, whichever comes first, any unused MATERIAL and DATA will either be destroyed in compliance with all applicable statutes and regulations or will be returned to the Provider as requested by the Provider.

9. ACKNOWLEDGEMENT. In all oral presentations or written publications resulting from the use of the MATERIAL and DATA, the Recipient will acknowledge the *<insert name of biospecimen resource>* as the source of the MATERIAL and DATA, unless requested otherwise by Provider, as follows:

“Biospecimens (and/or Derivatives) and associated data were provided by the *<insert name of biospecimen resource>*, an initiative developed through funding from the *<insert funding source, if applicable>*.”

10. COST AND SHIPPING. The MATERIAL and DATA are provided at no cost to Recipient. Provider will notify Recipient when the MATERIAL and DATA are ready for shipment. Recipient will be responsible for the pick-up and shipment, including shipping costs, of the MATERIAL and DATA.

The Parties have executed this Agreement by their respective duly authorized officers on the day and year hereinafter written. Any communication or notice to be given shall be forwarded in writing to the respective addresses listed below.

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Signature of Authorized Official **Date**

Certification of Provider Authorized Official: This Agreement __has / __has not been modified. If modified, the modifications are attached.

Signatures for Recipient

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Appendix 5. Example of Biospecimen Evidence-Based Practice

NCI Biospecimen Evidence-Based Practices		SNAP-FREEZING OF POST-SURGICAL TISSUE BIOSPECIMENS			
Author	BBRB	Revision Date		BEBP # 1	
Page #	Page 74 of 150	Effective Date		REV #0	

1.0 PURPOSE

The purpose of this document is to provide evidence-based guidance for the proper snap-freezing of human tissue biospecimens. This guidance is intended to support the development and execution of evidence-based Standard Operating Procedures (SOPs) for human biospecimen collection, processing, and storage operations.

2.0 SCOPE

This evidence-based best practice document is applicable to all human tissues that are to be preserved by snap-freezing. Biospecimens preserved under these procedural guidelines are suitable for downstream analysis of DNA, RNA, protein, and morphology endpoints. Additional analytical endpoints, including but not limited to cell viability, cell sorting, drug sensitivity testing, or use as donor specimens for xenografts or primary tissue culture, do not fall within the scope of this document.

3.0 DEFINITIONS

- 3.1** **Organ** – the complete or partial organ that is removed from the patient for dissection.
- 3.2** **Module** – the portion(s) of the organ that is/are specifically removed for the creation of segments or aliquots.
- 3.3** **Segment** – the component(s) that is/are dissected from the module that will be used to create the aliquot(s) for final labeling and submission.
- 3.4** **Aliquot** – the final tissue component(s) that is/are dissected directly from the organ or the segment according to protocol.
- 3.5** **Surgical Warm Ischemia Time** – the length of time a biospecimen is retained at physiological temperature, commencing with instrument-obstructed blood flow and terminating upon removal from the patient.
- 3.6** **Surgical Cold Ischemia Time** – the length of time elapsed between the time of removal of the tissue from the patient and the time the tissue is preserved by freezing, placement in formalin, or other stabilization method.
- 3.7** **Post-Mortem Interval (PMI)** – the length of time elapsed between the time of non-beating heart death and the time the tissue is preserved by freezing, placement in formalin, or other stabilization method.

4.0 ENVIRONMENTAL HEALTH & SAFETY

- 4.1** Universal Precautions (CDC-1978) are used for all phases of organ/tissue dissection and handling. Reference 9.1.1.

5.0 RECOMMENDED MATERIALS/EQUIPMENT

- 5.1 Plastic-backed absorbent bench paper.
- 5.2 New disposable dissecting equipment for each organ.
- 5.3 Liquid Nitrogen (LN2).
- 5.4 Dewar flask.
- 5.5 Cryogenic specimen storage container (cryovial, cryostraw, cryosette®, cryomold, or equivalent storage container designed for temperatures at or below -190°C), LN2 storage container or, in the event of immediate shipment, LN2 dry shipper.
- 5.6 Should LN2 be unavailable, alternative freezing media may include: isopentane pre-cooled with LN2; isopentane cooled with dry ice; dry ice alone; -80°C freezer. When utilizing dry ice or -80°C for freezing and storing at -80°C, suitable cryogenic specimen storage containers designed for temperatures at or below -80°C will be acceptable, and shipment may be performed on dry ice.

6.0 PROCEDURAL GUIDELINES

- 6.1 Recording of biospecimen preacquisition data
 - 6.1.1 Whenever possible, extensive data should be recorded relating to preacquisition conditions that may affect the integrity of the biospecimen. Such data may include patient information (including age, gender, diagnosis and treatment) as well as details relating to surgery and biospecimen acquisition (including the use of anesthesia, warm ischemia time, and surgical procedure and duration).
- 6.2 Preparation of freezing containers and bench space.
 - 6.2.1 Pre-labeled cryogenic specimen storage containers for each organ being dissected should be identified and arranged before the organ is available for dissection.
 - 6.2.2 Specimen containers should be appropriately labeled and organized, and tissues of different anatomic sites as well as tumor and normal tissues should be segregated to the extent possible.
 - 6.2.3 Clean disposable scalpels and forceps should be used when cutting different tissue types of the same patient and specimens from different patients. Contact with absorbent materials which may contaminate dissected research tissues or where capillary action may draw fluid from tissue samples should be avoided.
- 6.3 Post-collection storage of tissue specimens on wet ice.
 - 6.3.1 Specimens may be placed in a sterile closed container on wet ice until dissection (See 8.1).
- 6.4 Minimizing cold ischemia time.
 - 6.4.1 Dissection should be accomplished soon after the specimen is released by the supervising physician. Cold ischemia time should be minimized as much as possible, optimally less than 20 min but no more than 1 hour (See 8.2). Cold ischemia time should be documented for every module or segment and for each subsequent aliquot.
 - 6.4.2 For tissue specimens collected postmortem, PMI should be minimized as much as possible, optimally less than 2 hours, but no more than 6 hours (See 8.3). This time should be documented for every patient and attached to the module and its aliquots.
- 6.5 Dissection notes.
 - 6.5.1 Dissection should be performed one organ at a time. Final aliquots should be no thicker than 0.4 cm and placed into the proper cryogenic specimen storage containers. If morphological analysis is anticipated then specimens can be surrounded by OCT

medium prior to freezing; however, the use of OCT is not optimal for some specific molecular analysis methods (See 8.4).

6.6 Freezing of tissues.

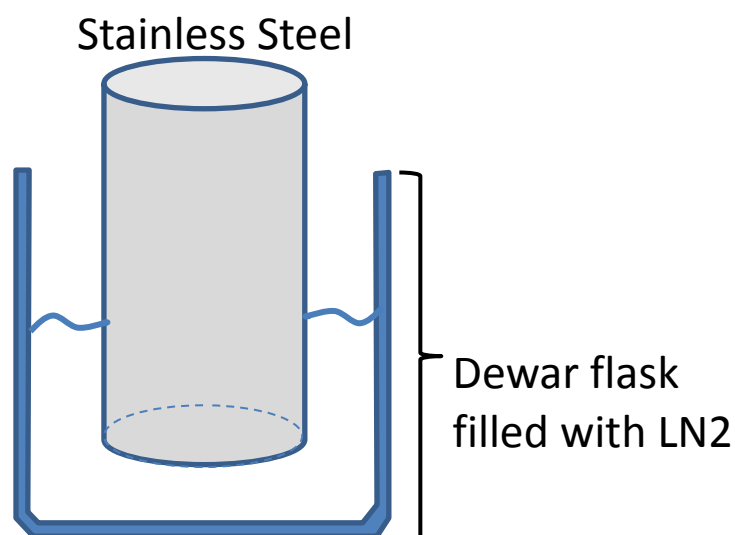
- 6.6.1** Optimally, the tightly sealed cryogenic specimen storage container should be frozen in LN2 vapor. This can be achieved by suspending a stainless steel beaker inside a bench top Dewar flask pre-filled with LN2 (See Figure 7.1). The specimen storage container should then be placed inside the steel beaker for 2 minutes or less depending on the size of the specimen (See 8.5). Common alternatives to freezing in LN2 vapor may include freezing by immersion in LN2 or immersion in isopentane pre-cooled to -80°C or below (See 8.6).
- 6.6.2** If LN2 is unavailable at the physical site where specimens are collected and preserved, alternative freezing methods may used, and include immersion in isopentane pre-cooled with dry ice, placement on dry ice, or placement in a -80°C freezer. Freezing specimens directly on dry ice should be avoided if they are to be used for morphological analysis (See 8.7).

6.7 Transfer and storage of frozen biospecimens.

- 6.7.1** After freezing, the cryogenic specimen storage container should be transferred for storage in a LN2 vapor freezer. Should LN2 be unavailable, specimen storage containers may be stored at -70°C or colder (See 8.8).
- 6.7.2** Alternatively, the frozen specimens may be placed directly into a LN2 dry shipper for immediate transport (See 8.8). Specimen containers frozen in LN2 and destined for storage in LN2 should be held in LN2 vapor before and during transfer to repository/long term storage. Should LN2 be unavailable, specimen storage containers may be shipped on dry ice. Specimen containers destined for storage at -80°C should be held on dry ice before and during transport.

7.0 FIGURES

7.1 Experimental set-up for snap-freezing in LN2 vapor



8.0 SUMMARIES OF LITERATURE EVIDENCE

- 8.1** Incubation of specimens on wet ice as opposed to room temperature reportedly delays the onset of ischemia-induced effects for RNA analyses [1-3], although data conflict as to whether incubation on wet ice [4] or at room temperature in the absence of buffer [5] is the optimal ischemic condition for protein preservation.

- 8.2** Cold ischemia has elicited quick and selective alterations in RNA transcript levels [6-8] and protein expression [4] after as little as 15-20 min at room temperature. Importantly, studies investigating similar timepoints extend the window of stability citing significant and selective changes after 30 min [6, 10], 60 min [10], 120 min [11], 6 h [1], or no change after 2 h [12,13] or 5 h [16]. Other analytical endpoints appear to be more robust, as a cold ischemia time of 60 min or less did not affect yields of DNA [9], RNA [15,16] or protein [9], PCR amplification of DNA targets [9], or DNA quality [9, 14] and evidence of protein degradation was first reported after 24 h at room temperature [11]. Similarly, cellular analysis by flow cytometry was not significantly affected by ischemia time of 4 h or more [17]. While reports conflict as to whether RNA quality is adversely affected by progressive ischemia the earliest reported onset of significant RNA degradation as determined by RIN was after 45 min at room temperature in thyroid and colon [18]. Additional variables confounding investigation of ischemia-induced effects on RNA quality include: (a) tissue-specific differences in the timing and magnitude of effect as significant RNA degradation has also been reported after 12 h in liver and 18 h in an ovarian carcinoma specimen [2], (b) increased variability among RNA integrity numbers (RIN) following 30 to 120 min of ischemia [8, 19], (c) tissue composition-dependent differences in RIN, with lower RINs reported for specimens rich in connective tissue [21], (d) manual versus automated extraction methods [21], (e) and analysis [22, 23].
- 8.3** PMI does not significantly alter DNA [24], RNA [24-28], or protein [24, 28] yields with a few notable tissue-specific exceptions in frontal cortex [24, 29] and spleen [31]. Although RNA degradation has been reported in autopsy specimens [26, 31], reports conflict as to whether there is no clear relationship between the degree of degradation and PMI [25, 28, 30-35] or whether a weak but significant negative correlation is present [29]. The majority of DNA and RNA [25, 26, 28, 30, 31, 34, 36, 37] and protein expression analyses [29], as well as protein methylation activity [38], do not appear to be affected by a PMI of 1-5 days or less.
- 8.4** DNA and RNA yields, RNA quality, PCR and RT-PCR analyses and immunohistochemistry and Western blot analyses generated equivalent results in OCT-embedded specimens immersed in isopentane pre-cooled with LN2 and case-matched controls preserved by immersion in LN2, suggesting these molecular and immunoassays are not adversely affected by the presence of OCT or isopentane [39]. Although OCT-embedding has been reported to interfere with subsequent PCR analysis of amplicons longer than 280 bp [40], a more recent study employing a column-based extraction method observed no deleterious effects of OCT on PCR analysis of amplicons ranging in length from 267-927 bp when compared to untreated controls snap frozen in LN2 [39]. Receptor binding capability as determined by radioligand-binding and ligand titration also produced equivalent results between OCT-embedded and unembedded controls [41], while interference due to OCT has been reported for the dextran-charcoal and Lowry Protein assays [42]. While OCT has also been shown to interfere with mass spectrometry-based proteomic analyses in an animal model [43], a recent study using a human cell line demonstrated that OCT compound can be successfully removed by ether-methanol precipitation or filter-aided sample preparation [45].
- 8.5** Superior morphology was observed when specimens were frozen in LN2 vapor using a double-walled vessel either alone [45] or in media [46] compared to those directly immersed in LN2 [45, 46] or on dry ice with a cooling device [46]. While cellular dehydration and extra- and intracellular ice crystal formation and their resultant artifacts occurred more prominently at cooling rates slower than LN2 (an estimated 2000°C/min) [47], direct immersion in LN2 can

result in the Leidenfrost effect, the creation of a insulating vapor layer upon contact with a substance hotter than the liquid's boiling point [48].

- 8.6** Specimens frozen by immersion in LN2 or isopentane pre-cooled to -80°C produced comparable DNA, RNA and protein yields; RNA purity and integrity; and RNA and protein expression levels [39]. However, morphology was modestly superior among specimens immersed in isopentane pre-cooled to -80°C than those immersed in LN2 [39], but morphology was equivalent among specimens frozen in isopentane pre-cooled with either LN2, dry ice, or a -100 °C freezer [49].
- 8.7** Specimens frozen by placement in a -70°C freezer or immersion in LN2 produced comparable RNA quality and were successfully used in the construction of a cDNA library [28]; and specimens frozen in a -20°C or -70°C freezer displayed epidermal growth factor receptor (EGFR) activity that was comparable to specimens immersed in LN2 [50]. However, freezing specimens on dry ice using a cooling device [45] or by the carbon dioxide quick freeze method [39] compromised morphology in comparison to LN2 due to the formation of macro- and microscopic cracks. Similarly, microscopic and ultrastructural damage due to ice crystal formation were more prevalent among specimens embedded in OCT and frozen in a -20°C cryostat compared to those immersed in isopentane pre-cooled to -60°C [51, 52] or -112°C [53], although effects may be influenced by tissue type [51].
- 8.8** Potential effects of storage temperature on DNA and RNA analyses have not been investigated. Although EGF-R activity was reduced by the initial freeze, short term storage for up to 21 days at -20°C, -70°C, or LN2 produced equivalent results [54]. Specimens stored in a LN vapor freezer or at -80°C displayed similar gross morphology and equivalent levels of rubidium, iron, and zinc [55].
- 8.9** Potential effects of the temperature and conditions of shipment on DNA, RNA, and morphological analyses have not been investigated. Shipment of breast cancer specimens on dry ice, as opposed to in a LN2 dry shipper, resulted in a reduction in ER binding and a subsequently lower incidence of ER-positive cases [56].

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<http://www.cdc.gov/mmwr/preview/mmwrhtml/00000039.htm>; Tools for Protecting Healthcare Personnel, CDC: <http://www.cdc.gov/HAI/prevent/ppe.html>.
- 9.1.2** CLSI IL-28A: Quality Assurance for Design Control and Implementation of Immunohistochemistry Assays; Approved Guideline—Second Edition S Hewitt, personal communications, draft CLSI IL-28a.
- 9.1.3** CLSI MM13-A: Collection, Transport, Preparation, and Storage of Specimens for Molecular Methods; Approved Guideline. 2008. Vol25, No 31.
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Appendix 6: CAP Biorepository Accreditation Program Checklist

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Biorepository Checklist



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SUMMARY OF CHECKLIST EDITION CHANGES

Biorepository Checklist

04/21/2014 Edition

The information below includes a listing of checklist requirements with significant changes in the current edition and previous edition of this checklist. The list is separated into three categories:

1. New
2. Revised:
 - Modifications that may require a change in policy, procedure, or process for continued compliance; or
 - A change to the Phase
3. Deleted/Moved/Merged:
 - Deleted
 - Moved — Relocation of a requirement into a different checklist (requirements that have been resequenced within the same checklist are not listed)
 - Merged — The combining of similar requirements

NOTE: The listing of requirements below is from the Master version of the checklist. The customized checklist version created for on-site inspections and self-evaluations may not list all of these requirements.

NEW Checklist Requirements

<u>Requirement</u>	<u>Effective Date</u>
BAP.01525	07/29/2013
BAP.06802	07/29/2013
BAP.06804	07/29/2013
BAP.06806	07/29/2013
BAP.06808	07/29/2013
BAP.06810	07/29/2013
BAP.06812	07/29/2013
BAP.06816	07/29/2013
BAP.06818	07/29/2013
BAP.06819	04/21/2014
BAP.06820	07/29/2013
BAP.06824	07/29/2013
BAP.06826	07/29/2013

BAP.06828	07/29/2013
BAP.06830	07/29/2013
BAP.06832	07/29/2013
BAP.06834	07/29/2013
BAP.06836	07/29/2013
BAP.06838	07/29/2013
BAP.06840	07/29/2013
BAP.06844	07/29/2013
BAP.06846	07/29/2013
BAP.06848	07/29/2013
BAP.06850	07/29/2013
BAP.06854	07/29/2013
BAP.06856	07/29/2013
BAP.06858	07/29/2013
BAP.06860	07/29/2013
BAP.06880	04/21/2014
BAP.07110	04/21/2014
BAP.07120	07/29/2013
BAP.07210	04/21/2014
BAP.07220	04/21/2014
BAP.13740	04/21/2014

REVISED Checklist Requirements

<u>Requirement</u>	<u>Effective Date</u>
BAP.01700	07/29/2013
BAP.02500	07/29/2013
BAP.06900	04/21/2014
BAP.08000	07/29/2013
BAP.08700	07/29/2013
BAP.09300	07/29/2013
BAP.09600	07/29/2013
BAP.09700	07/29/2013
BAP.12800	07/29/2013

DELETED/MOVED/MERGED Checklist Requirements

<u>Requirement</u>	<u>Effective Date</u>
BAP.04600	07/28/2013
BAP.07000	04/20/2014
BAP.07700	07/28/2013

INTRODUCTION

A biorepository is defined as an entity that receives, stores, processes, and/or disseminates biospecimens, their derivatives and relevant data, as needed. It encompasses the physical location as well as the full range of activities associated with its operation. This checklist covers a broad range of activities that occur in biorepositories. Not all checklist requirements will apply to every biorepository.*

The scope of services of the biorepository must be clearly documented.

*References used in the development of this checklist were the CAP Accreditation Checklists, 2012 Best Practices for Repositories (ISBER**), and the NCI Best Practices for Biospecimen Resources.*

*Biorepository — For the sake of consistency, biorepository will be used throughout this checklist and may be considered synonymous with biobank and repository.

**ISBER — International Society for Biological and Environmental Repositories is an international forum that addresses the technical, legal, ethical, and managerial issues relevant to repositories of biological and environmental specimens.

DEFINITION OF TERMS

Aliquot - Process wherein a specimen is divided into separate parts which are typically stored in separate containers as individual samples. The term aliquot may also be used as a noun to denote a single sample.

Anonymization - The process of removing particulars from samples, test results, or records to prevent traceability to the original patient

Blinding - An action taken to prevent access to information that might affect the outcome of an observation

Coded specimen - Identifying information (such as name or social security number) that would enable the investigator to ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (*i.e.* the code); and a key to decipher the code exists, enabling linkage of the identifying information to the private information of specimens

De-identify - The removal from a specimen of all 18 elements that could be used to identify the individual or the individual's relatives, employers, or household members; these elements are enumerated in the HIPAA Privacy Rule

Derivative - A substance that can be made from another substance

Equipment - Single apparatus or set of devices or apparatuses needed to perform a specific task

Function check - The set of routines that show an instrument to be ready for operation

Instrument - An analytical unit that uses samples to perform chemical or physical assays

Legacy specimen - Biospecimens available for research once all protocol-specified endpoints, including clinical and biorepository studies, have been completed. These remaining biospecimens could be made

available by the biorepository for correlative studies (subject to application, scientific review, and approval).

Maintenance - Those activities that prolong the life of an instrument or minimize breakdowns or mechanical malfunctions. Examples include cleaning, changing parts, fluids, tubing, lubrication, electronic checks, etc.

Material Transfer Agreement (MTA) - An agreement that governs the transfer of tangible research material and associated clinical data between two organizations, when the recipient intends to use it for his/her own research purposes

Performance verification - The set of processes that demonstrate an instrument to run according to expectations

Quality assurance - The systematic monitoring and evaluation of the various aspects of a project, process, service or facility to maximize the probability that minimum standards of quality are being attained

Quality control - An integral component of *quality management* composed of the aggregate of processes and techniques used to detect, reduce, and correct deficiencies in an analytical process

Quality control (QC) is a surveillance process in which the actions of people and performance of equipment and materials are observed in some systematic, periodic way that provides a record of consistency of performance and action taken when performance does not conform to standards set by the biorepository. QC is a set of procedures designed to monitor the test method and the results to assure test system performance; QC includes testing control materials, charting the results and analyzing them to identify sources of error, and determining, performing and documenting any remedial action taken as a result of this analysis.

Remnant specimens - Remaining portion of a specimen obtained for clinical purposes that is no longer needed for its original purpose and that would otherwise be discarded

Sample - A single unit containing material derived from one specimen

Specimen - A specific tissue, blood sample, etc. taken from a single subject or donor at a specific time

Source Facility - Those sites that contribute specimens to the biobank. The source facility may be a clinic, hospital or individual investigator, and, in some instances, the biorepository may be the source facility, (e.g. when the biorepository does blood or specimen collections for normal controls).




BIOREPOSITORY

QUALITY MANAGEMENT

PROCEDURE MANUAL

Inspector Instructions:

- | | |
|--|---|
| | <ul style="list-style-type: none">• Representative sample of procedures for completeness and laboratory director review. Current practice must match contents of procedures/policies.• Privacy and confidentiality policies and procedures |
|--|---|

	
	<ul style="list-style-type: none"> • How do you access procedures? • What procedure has most recently been implemented or modified? • How do you ensure all copies of procedures are up to date? • How are changes in procedures documented and communicated to staff? • How does the facility protect patient information?
	<ul style="list-style-type: none"> • Identify a newly implemented procedure in the prior two years and follow the steps through authoring, director review and staff training

BAP.01000 Procedure Manual

Phase II

A complete procedure manual is available at the workbench or in the work area.

NOTE 1: The use of inserts provided by manufacturers is not acceptable in place of a procedure manual. However, such inserts may be used as part of a procedure description, if the insert accurately and precisely describes the procedure as performed in the biorepository. Any variation from this printed or electronic procedure must be detailed in the procedure manual. In all cases, appropriate reviews must occur.

NOTE 2: A manufacturer's procedure manual for an instrument/reagent system may be acceptable as a component of the overall departmental procedures. Any modification to or deviation from the procedure manual must be clearly documented.

NOTE 3: Card files or similar systems that summarize key information are acceptable for use as quick reference at the workbench provided that:

- A complete manual is available for reference
- The card file or similar system corresponds to the complete manual and is subject to document control

NOTE 4: Electronic (computerized) manuals are fully acceptable. There is no requirement for paper copies to be available for the routine operation of the biorepository so long as the electronic versions are readily available to all personnel. However, procedures must be available to biorepository personnel when the electronic versions are inaccessible (e.g. during biorepository information system or network downtime); thus, the biorepository must maintain either paper copies or electronic copies on CD or other media that can be accessed via designated computers. All procedures, in either electronic or paper form, must be readily available for review by the inspector at the time of the CAP inspection.

Electronic versions of procedures must be subjected to proper document control (i.e., only authorized persons may make changes, changes are dated/signed (manual or electronic), and there is documentation of review). Documentation of review of electronic procedures may be accomplished by including statements such as "reviewed by [name of reviewer] on [date of review]" in the electronic record. Alternatively, paper review sheets may be used to document review of electronic procedures. Documentation of review by a secure electronic signature is NOT required.

REFERENCES

1) Clinical and Laboratory Standards Institute (CLSI). Quality Management System: Development and Management of Laboratory Documents; Approved Guideline - Sixth Edition. CLSI document QMS02-A6 (ISBN 1-56238-869-X). Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087 USA, 2013.

BAP.01100 Policy/Procedure - Confidentiality Phase II

Policies and procedures are in place to minimize the risk to individuals from whom the specimens and data were obtained and to protect their privacy and confidentiality.

BAP.01200 Policy/Procedure Review Phase II

There is documentation of review of all policies and procedures every two years by the current director or designee.

NOTE: The director must ensure that the collection of policies and technical protocols is complete, current, and has been thoroughly reviewed by a knowledgeable person. Technical approaches must be scientifically valid and clinically relevant. To minimize the burden on the biorepository and reviewer(s), it is suggested that a schedule be developed whereby roughly 1/24 of all procedures are reviewed monthly. Paper/electronic signature review must be at the level of each procedure, or as multiple signatures on a listing of named procedures. A single signature on a Title Page or Index of all procedures is not sufficient documentation that each procedure has been carefully reviewed. Signature or initials on each page of a procedure is not required.

Only policies and procedures are addressed in this requirement. Biennial review is not required for other controlled documents.

BAP.01300 New Procedure Review Phase II

The director reviews and approves all new policies and procedures, as well as substantial changes to existing documents, before implementation.

NOTE: Current practice must match the policy and procedure documents.

BAP.01400 New Director Procedure Review Phase II

If there is a change in directorship of the biorepository, the new director ensures (over a reasonable period of time) that biorepository procedures are well documented and undergo an appropriate review.

BAP.01500 Knowledge of Procedures Phase II

The biorepository has a system documenting that all personnel are knowledgeable about the contents of procedure manuals (including changes) relevant to the scope of their biorepository activities.

NOTE: This does not specifically require annual procedure sign-off by testing personnel. The form of this system is at the discretion of the director.

Evidence of Compliance:



- ✓ Relevant quizzes and results **OR** documentation of competency **AND**
- ✓ Systems to document policy/procedure changes **AND**
- ✓ Documentation of receipt/training in either paper or electronic format

When a procedure is discontinued or replaced, a paper or electronic copy is maintained for at least 2 years, recording initial date of use, and retirement date.

SPECIMEN HANDLING

The collection, processing, embedding, and quality check for all biospecimens is critical to the overall quality and diversity of the sample inventory.

Inspector Instructions:

	<ul style="list-style-type: none"> • Sampling of policies and procedures for sample handling, including sample types, samples with potentially infectious materials, aliquoting, relabeling, de-identifying or anonymizing, and specimen retrieval • Policy for the type of samples suitable for submission to the biorepository • Sampling of records for the assessment of the quality of stored specimens • Specimen rejection criteria policy and records of rejection • Records of informed consent and IRB releases
	<ul style="list-style-type: none"> • Specimen processing area for clean environment • Aliquot sizes of specimens • Specimen identifiers • Specimen storage conditions during sample receipt and processing • Tracking of samples as they move from one station to another
	<ul style="list-style-type: none"> • How does your biorepository maintain and track temperature excursion information? • Explain your quality assessment process for stored specimens • How is the risk of specimen misidentification monitored and the process improved? • What is your specimen coding system for sample identification? • How do you confirm patient consent prior to processing and banking? • What do you do if the sample size is too small relative to the requirements or it does not meet researchers' needs?
	<ul style="list-style-type: none"> • Follow a tissue sample released for research from the pathologist to storage, verifying specimen identification throughout the process. • Select several specimens and follow their tracking throughout the life of the specimen, including from parent to child, etc.

There is a clearly defined policy defining types of specimens submitted to the biorepository that is based on:

1. Purpose - intended use of specimen
2. Required specimen data
3. Safety - laboratories are suitable for the type of specimen/pathogen requiring processing (biosafety/risk level)
4. Duration of storage (may be indefinite)

NOTE: The policy may be an overarching statement that defines the criteria required for all collections held in the biorepository. This may include the receipt or transfer of an entire collection.

REFERENCES

- 1) Biosafety in Microbiological and Biomedical Laboratories, 5th Edition, HHS Publication No. (CDC) 21-1112 Revised December 2009 (<http://www.cdc.gov/biosafety/publications/bmbl5/BMBL.pdf>)

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BAP.01700 Collection/Processing Oversight

Phase II

A pathologist or designee assigned to the management of the biospecimens must ensure that the documented collection processes and policies reflect published best practices.

NOTE: Blood and other body fluids not required for the diagnosis or prognosis must be collected with approved protocols and may not require pathologist review. To determine remnant tissue at the site of the collection, the appropriate medical/legal designee must be involved in the decision. This does not apply to downstream processing.

If samples are acquired according to sponsor-driven protocols, the sponsor makes all decisions about sample usability. The biorepository carries out the instructions provided by the sponsor. In this instance BAP.01700 is not applicable.

REFERENCES

- 1) 2012 Best Practices for Repositories, Cell Preservation Technology, Vol. 10, Num 2, <http://www.isber.org/bp/documents/ISBERBestPractices3rdedition.pdf>

BAP.01800 Quality Control/Quality Assurance for Stored Specimens

Phase II

A mechanism for periodic assessment of the quality of stored specimens is in place for each class of biospecimens in the biorepository.

NOTE: The frequency of the checks may be determined by the

1. Type of specimens being stored
2. Preservation method
3. Turnover of the material

This may take a variety of forms including direct observation of materials, sampling, integrity of records, etc. The form and frequency that this takes is to be defined by the biorepository.

Quality assurance may be assessed at the time of disbursement.

Evidence of Compliance:

- ✓ Documentation of inventory sampling **OR**
- ✓ Documentation of unsuitable specimens by collection, as applicable **OR**
- ✓ Documentation of inventory QA/QC processes **OR**
- ✓ Assessment from researchers using the specimens

BAP.01900 Aliquot Size Phase II

Aliquot sizes are appropriate for the intended use of the specimen.

NOTE: Freeze/thaw cycles may be deleterious to the macromolecules intended for analysis; therefore, it is important to provide some aliquots that have a suitable volume for single-use. Storage and cost logistics may require that some larger volume aliquots are maintained.

Evidence of Compliance:

- ✓ Documentation of sample size stated in protocols

BAP.02000 Temperature Excursions Phase II

Temperature excursions beyond recommended storage requirements are tracked during routine processing and distribution.

NOTE: The biorepository has all known relevant annotations on a given biospecimen that may be made available to the researcher.

BAP.02100 Clean Environment Phase II

Specimens are processed in a clean environment, when required.

NOTE: RNA is particularly sensitive to RNases that may be present on tools and surfaces that have not been sterilized.

BAP.02200 Biological Safety Cabinet Phase II

Aliquots are made using sterile pipettes within a biological safety cabinet, when required.

BAP.02300 Policy for Handling Specimens for Infectious Diseases Phase II

There is a policy for receipt and management of potentially infectious material that includes application of universal precautions.

NOTE: Elements of the policy must include proper handling of specimens for biohazard protection. The policy may include information about prior testing for infectious hazards.

REFERENCES

- 1) OSHA regulation 29CFR1910.1020.

BAP.02400 Surgical Pathology Specimens Release for Research Phase II

A sample of a surgical pathology gross specimen may be submitted for research only if all of the following criteria are met.

1. The pathologist determines that the sample(s) is not necessary for diagnostic purposes.
2. For laboratories subject to US regulations, formal written authorization is obtained in accordance with the requirements of HIPAA if identifiable patient information is released.
3. The biorepository meets other relevant requirements, including but not limited to, the requirements of the institution, the directives of any applicable institutional review board (IRB) or similar entity, and state and

- local laws and regulations.
4. De-identified/anonymized sample of a surgical pathology gross specimen may be submitted for research if a waiver of consent has been obtained.

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BAP.02500 Histological Characteristic Review

Phase II

A pathologist reviews all solid tissue specimens to determine the histological characteristics of the specimens that are submitted to the biorepository.

NOTE: Characteristics may vary depending on the tissue type and the nature of any pathological changes (when present). For example, solid tissue specimens from the colon of a patient with ulcerative colitis and colonic adenocarcinoma may include a section of normal colon, a section of colon involved by the chronic active inflammatory process, and a section from the colonic adenocarcinoma. Solid tissue samples can be banked and/or processed according to the previously established protocol for handling normal, disease involved, and neoplastic colonic tissue. Pathology review may occur prior to banking or distribution.

BAP.02600 Specimen Identity

Phase II

The identity of every specimen is maintained through each step of processing and slide preparation.

NOTE: An unambiguous system of unique specimen identification coupled with a legible, sequential container labeling system that withstands exposure to anticipated reagents and temperature extremes are essential to fulfill this requirement. Containers can be various shapes and sizes and constructed from multiple materials (plastic, glass, cardboard). It is important to ensure that the container is suitable for the type of specimen and how it will be used/stored.

BAP.02700 Misidentification Risk

Phase II

The biorepository has a documented procedure to ensure that the risk of misidentification is monitored and subjected to continual process improvement.

NOTE: The biorepository must actively monitor the key elements of all sample types throughout the entire process. The program may include, but is not limited to: 1) maintaining identification of nucleic acids and protein derivatives from a biospecimen, 2) QC and application of a barcode or other identifier, and 3) record of the number of sample derivatives prepared.

BAP.02800 Unique Identifier

Phase II

Each specimen received into the biorepository receives a unique identifier.

BAP.02900 Specimen Tracking Mechanism

Phase II

The identity of every specimen is maintained and tracked throughout the life of the specimen and its derivatives, e.g. parent to children to grandchildren, etc.

NOTE: An effective tracking system must be in place to ensure that biospecimens can be tracked accurately from the collection site through biospecimen arrival and subsequent

shipment from the biorepository.

BAP.03000 Specimen Rejection Criteria Phase II

There are documented criteria for the condition exceptions that should be recorded and communicated to researchers regarding items that could impact research results.

NOTE: This requirement is not intended to imply that all "unacceptable" specimens be discarded or not analyzed. For example, if an unacceptable specimen is received, there must be a mechanism to notify the requesting researcher, and to note the condition of the sample on the report. For example, many semen samples are sub-optimal; all samples should be evaluated and unusual properties noted. The biorepository may wish to record that a dialogue was held with the requesting researcher.

BAP.03100 Relabeling Phase II

There is a procedure in place for relabeling of a biospecimen and/or aliquots.

NOTE: Circumstances under which relabeling may occur may include, but are not limited to: a) inadvertent duplication of ID from internal or external sources; b) for full de-identification; c) replacement of a label (e.g. original label has fallen off).

Evidence of Compliance:

✓ Documentation of reason for relabeling

BAP.03200 De-identification for Research Phase II

For specimens that are released for research, there is a procedure for de-identifying/blinding or anonymizing specimens without compromise to research-related demographic information, when required.

BAP.03300 Coding Phase II

There is a defined coding system for sample identification.

BAP.03400 Participation/Donor Informed Consent Phase II

For specimens that are released to a biorepository, appropriate participant/donor informed consent is secured.

NOTE: This is not applicable when specimens are obtained under waiver of consent.

BAP.03500 IRB Release Phase II

For specimens that are released to a biorepository, an appropriate IRB release is in place.

BAP.03600 Specimen Collection/Handling Protocol Phase II

Collection, processing, and storage times are documented as required by the

biorepository protocol in place at the time of biospecimen procurement.

NOTE: Time is kept to a minimum between when a specimen is removed from its site of origin and when it is preserved (e.g. fixed, cooled, or frozen).

BAP.03700 Retrieval Procedures

Phase II

All specimen retrieval procedures ensure specimen integrity.

NOTE: The integrity of the biospecimen must be maintained throughout the retrieval process.

Evidence of Compliance:

- ✓ Procedure defining the process

BAP.03800 Paraffin Embedding and/or Fixation QC



Phase II

The biorepository has a procedure for paraffin embedding and/or fixation and quality checks to include the frequency requirements for quality checks (e.g. 24 hours/48 hours).

NOTE: This requirement applies only to biorepositories that perform their own fixation and embedding and are not a part of a CAP-accredited laboratory.

STORAGE

Inspector Instructions:

	<ul style="list-style-type: none"> • Sampling of policies and procedures for specimen storage conditions • Storage temperature records
	<ul style="list-style-type: none"> • Sampling of stored specimens for temperatures required by protocols

BAP.03900 Tissue Storage Conditions

Phase II

The procedure manual defines the necessary storage conditions of the different specimens handled, all required records and policies, and a protocol for return of each specimen type to storage after issuance for use, as appropriate.

BAP.04000 Tissue Storage Temperature




Phase II

The records show that specimens were stored at the protocol-required temperature.

NOTE: Storage of specimens must be appropriate for the type of specimens and its means of preservation. Failure to adhere to requirements could result in a specimen not being suitable for the purpose for which it was intended.

PRESERVATION

Inspector Instructions:

	<ul style="list-style-type: none"> • Sampling of biospecimen QA reports for key elements of processing and preservation of solid and fluid specimens
	<ul style="list-style-type: none"> • If collection occurs on-site, observe the processing/preservation procedure
	<ul style="list-style-type: none"> • How does your biorepository capture variables that could impact biospecimen usage? • How/when would the biorepository communicate pre-analytic variables to researchers? • How do you ensure accuracy of pre-analytic data capture?

BAP.04100 Pre-Analytic Variables

Phase II

There is a mechanism to capture pre-analytical variables that could impact potential uses of the specimens.

NOTE: While intended use of specimens is not always known, the specimens are typically stored for anticipated types of analysis (i.e. serology, molecular, proteomic) and should be fit for purpose for the anticipated applications. Preservation procedures are optimized for the greatest number of molecular analytes/analysis platforms.

REFERENCES

- 1) Standard Preanalytical Coding for Biospecimens: Defining the Sample PREanalytical Code, Betsou, *et al*, *Cancer Epidemiol Biomarkers Prev* April 2010 19; 1004.

BAP.04200 Processing/Preservation - Solid Specimens

Phase II

The key elements related to the processing and preservation of solid specimens are documented in the biospecimen QA report, when available.

NOTE: These elements may include, but are not limited to:

1. Chilling/heating/drying of tissue during handling
2. Size and number of tissue pieces
3. Percentage of tumor/necrosis/stroma in the tissue
4. Liquid collection media
5. Use of gauze wrapping, additives, and embedding compounds
6. Variation in fixation (e.g. temperature, buffer, pH of formalin, start/end time in fixative)
7. Freezing protocols
8. Time in fixative
9. Time to preserve

The biorepository has all known relevant annotations on a given biospecimen that may be

made available to the researcher. Information regarding some of these elements may not be available to the biorepository for all biospecimen collections, especially those that were procured before recent best practices for biorepositories were published.

BAP.04300 Processing/Preservation - Fluid Biospecimens

Phase II

The key elements related to the processing and preservation of fluid biospecimens are documented.

NOTE: Key elements may include, but are not limited to:

1. Collection preservative
2. Original volume received
3. Temperature and duration of specimen prior to processing
4. Temperature and speed of first centrifugation step
5. Temperature and speed of subsequent separation steps
6. Method used for separation
7. Derivative(s) preserved and their volume
8. Quality control results for derivatives (i.e. cell viability, purity, hemolysis status, human versus non-human content)
9. Tumor content (%), if applicable

The biorepository has all known relevant annotations on a given biospecimen that may be made available to the researcher. Under some circumstances some of this information may be "unknown" depending on the site and age of specimen. It is recommended that the biorepository encourage their source sites to gather/provide as much information as possible.




REFERENCES

- 1) Standard Preanalytical Coding for Biospecimens: Defining the Sample PREanalytical Code, Betsou, *et al*, *Cancer Epidemiol Biomarkers Prev* April 2010 19; 1004.

SPECIMEN PROCESSING

DNA/RNA EXTRACTION/AMPLIFICATION

Inspector Instructions:

	<ul style="list-style-type: none"> • Sampling of DNA/RNA extraction and amplification policies and procedures • Records of DNA quantity measurement • Records of nucleic acid integrity and purity assessment • Records of internal controls
	<ul style="list-style-type: none"> • Nucleic acid amplification procedures for proper physical containment and procedural controls to prevent carryover • Observe quantitation and quality control assessments
	<ul style="list-style-type: none"> • How is adequacy of nucleic acid isolation and preparation evaluated? How often is this done?



- Follow a sample from extraction through storage

BAP.04500 Specimen Identification

Phase II

There is a system to positively identify all participant specimens, specimen types, and aliquots through all phases of the analysis, including specimen receipt, nucleic acid extraction, nucleic acid quantification, hybridization, detection, documentation, and storage.

BAP.04700 Extraction/Purification Methods

Phase II

Nucleic acids are extracted and purified by methods reported in the literature, by an established commercially available kit or instrument, or by a validation of a method developed in-house.

NOTE: The method should be assessed for its suitability for each source type that requires extraction. Any modification to established procedures must be documented, as well as variations to procedures depending on anatomic site and biospecimen preservation format (e.g. fresh frozen vs. OCT-embedded).

Evidence of Compliance:

- ✓ Written procedure for each extraction process

BAP.04800 Nucleic Acid Quantity

Phase II

The quantity of nucleic acid is measured.

NOTE: The quantity of nucleic acid must be measured prior to use by a standard procedure that allows for the accurate determination of the concentration/quantity of the nucleic acid.

Evidence of Compliance:

- ✓ Records detailing the concentration and yield of nucleic acid per specimen, per extraction

BAP.04900 Human/Non-Human DNA

Phase I

When the downstream application requires an estimation of the ratio of human versus non-human genomic DNA in the specimen, the human/non-human DNA quantity is measured.

BAP.05000 Integrity/Purity Assessment - Nucleic Acids

Phase II

The integrity and purity of nucleic acid is assessed, when appropriate for downstream use.

NOTE: Standard measure for DNA purity is A260/280 ratio of 1.6 to 2.0. Values less than 1.6 are indicative of protein contamination and values of >2.0 are indicative of RNA

contamination. RNA should have A260/280 ratio of greater than 2.0. Analytical measures of nucleic acids include, but are not limited to: A260/280 spectrophotometric ratio, RNA-specific measures, double-stranded DNA (dsDNA), or integrity by agarose gel-electrophoresis. RNA integrity assessments should be determined if such a quality indicator would exclude samples from specific downstream methodologies.

RNA in specimens is highly labile because RNase is ubiquitous and difficult to inhibit. For human RNA targets, RNA quality must be assessed. However, depending on the target, it may not be necessary for all specimens to be assessed for RNA quality. RNA quality is not assessed, for example, for many types of viral RNA targets; however, the false negative rate must be documented.

BAP.05100 Neoplastic Cell Content Assessment

Phase II

There is documentation of histological assessment of neoplastic cell content for tumor specimens from which DNA or RNA is extracted for analysis.

NOTE: In addition to confirming the presence or absence of neoplastic cells by a pathologist, it may be necessary for some assays to assess neoplastic cellularity for some downstream assay to ensure that the percentage of neoplastic cells exceeds the limit of detection for the assay.

A corresponding H&E section from the same tissue block used for DNA or RNA extraction may be used to assess sample adequacy. In the case of a frozen tissue block, a validation formalin-fixed paraffin-embedded mirrored to the frozen tissue specimen may be used for histological examination of sample adequacy. Alternatively, a stain such as toluidine blue may be used to stain the slide that is being used for DNA extraction. When assessment of sample adequacy is performed outside of the testing facility, documentation of such assessment should accompany the sample.

BAP.05200 Carryover

Phase II

Nucleic acid amplification procedures (e.g. PCR) are designed to minimize carryover (false positive results) using appropriate physical containment and procedural controls.

NOTE: This item is primarily directed at ensuring adequate physical separation of pre- and post-amplification samples to avoid amplicon contamination. The extreme sensitivity of amplification systems requires that special precautions are taken. For example, pre- and post-amplification samples should be manipulated in physically separate areas; gloves must be worn and frequently changed during processing; dedicated pipettes (positive displacement type or with aerosol barrier tips) must be used; and manipulations must minimize aerosolization. In a given run, specimens should be ordered in the following sequence: participant samples, positive controls, negative controls (including "no template" controls in which target DNA is omitted and therefore no product is expected). Enzymatic destruction of amplification products is often helpful, as is real-time measurement of products to avoid manual manipulation of amplification products.

BAP.05300 Internal Controls Nucleic Acid Amplification

Phase II

In all nucleic acid amplification procedures, internal controls are run to detect a false negative reaction secondary to extraction failure or the presence of an inhibitor, when appropriate.



NOTE: The facility should be able to distinguish a true negative result from a false negative due to failure of extraction or amplification. Demonstration that another sequence can be

successfully amplified in the same specimen should be sufficient to resolve this issue. For quantitative amplification assays, the effect of partial inhibition must also be addressed.

The internal control should not be smaller than the target amplicon. There are some rare exceptions to this rule due to sequence length and design. In this situation the internal control should not be more than 10% smaller than the target amplicon and the use of a smaller internal control should be justified.

DIGITAL IMAGE CAPTURE

Inspector Instructions:

	<ul style="list-style-type: none"> • Sampling of qualification data
	<ul style="list-style-type: none"> • If significant differences in slide/staining characteristics are expected, how has the qualification taken this into account? • If clear digital images cannot be obtained, what is the process for determining the cause and correcting any potential problems with the scanning system? • What is done if tumor content is insufficient?

BAP.05400 System Qualification



Phase II



If digital whole slide imaging is used as an integral part of the biorepository operation, there is documentation that the system has been qualified for the intended use.

TISSUE MICROARRAY (TMA)

TMA technology helps expedite discovery of the novel targets important in disease treatment by providing a tool for high-throughput screening of multiple tissues using immunohistochemical, in situ hybridization, and fluorescent in situ hybridization (FISH) analyses. (Reference: <https://ccrod.cancer.gov/confluence/display/CCRTARP/About>)

Inspector Instructions:

	<ul style="list-style-type: none"> • Sampling of tissue microarray policies and procedures • Records of methods selected for region of interest of tissue and communication with the microarray technologist
	<ul style="list-style-type: none"> • System to positively identify specimens, specimen types and aliquots throughout the process

	<ul style="list-style-type: none"> • Who is responsible for selecting tissues and performing analysis for tissue microarray? • How are the selection and number of cores determined?
	<ul style="list-style-type: none"> • Follow a tissue specimen for TMA from processing to final analysis. Observe specimen identification, core selection and analysis.

BAP.05500 Specimen Identification

Phase II

There is a system to positively identify all participant specimens, specimen types, and aliquots through all phases of the analysis.

NOTE: The phases include, but are not limited to:

1. Specimen receipt
2. Specimen ID key
3. Tissue core selection from parent paraffin block
4. Location and identification within the new tissue microarray recipient tissue block
5. Documentation
6. Utilization (number of times sectioned)
7. Storage

BAP.05600 Preparation Procedures

Phase II

There is documentation describing the tissue types and purpose for the TMA, including the size and placement of the tissue cores as well as control tissue cores.

NOTE: Criteria for selection and documentation of the tissue cases are required. The usefulness and analysis of tissue microarray cores can be affected by the location (edges versus center) and loss of tissue cores as the tissue microarray block is thin sectioned. Consideration is of size, frequency, and location of cores therefore, should be considered and documented to match the intended use of the tissue microarray. Examples of the intended purpose of the TMA include, but are not limited to, disease-specific TMA, disease-progression TMA, tissue staining control TMA, cell line TMA, etc.

BAP.05700 Original Paraffin Tissue Block

Phase II

Policies are in place to determine to what extent the original paraffin tissue block lesion can be removed.

BAP.05800 Tissue Core Selection

Phase II

Tissues selected (paraffin block and tissue region of interest) to make a TMA must be selected by a qualified anatomic pathologist.

BAP.05900 Method of Core Selection Phase II

Methods of the selection of the regions of interest of tissue and clear documentation to transfer the correct information to a tissue microarray technologist must be documented.

BAP.06000 Number of Cores Phase II

Methods for determining the relevant number of cores to accurately represent the parent tissue block must be documented.

NOTE: A procedure is in place to determine the optimum number of cores required per TMA as dictated by each study protocol.

BAP.06100 Tissue Microarray Procedure Phase II

There is a procedure to ensure that the correct tissue is placed in the correct location of the TMA, for example, a TMA map (tissue type, key ID, and location in the TMA).

NOTE: This would include the placement and location of tissue controls and orientation markers.

There is software available to manage the map of a TMA. This resource is very useful in helping the pathologist evaluate and read results from the TMA after it has been stained.

BAP.06200 TMA Evaluation Phase I


Analysis of TMAs are performed by an anatomic pathologist and documented.



NOTE: The analysis may include software-assisted analysis or manual reading by a pathologist.

LASER CAPTURE MICRODISSECTION (LCM)

LCM "captured" cells can be used in a wide range of downstream assays such as loss of heterozygosity (LOH) studies, gene expression analysis at the mRNA level or in a wide range of proteomic assays such as 2D gel analysis, Western blotting, reverse phase protein array, and surface-enhanced laser desorption ionization (SELDI) protein profiling. Commercial kits for the isolation of RNA and DNA are available and adaptable to the micro samples obtained by LCM. (Reference: <http://home.ccr.cancer.gov/LOP/Research/lcm/Default.asp>)

Inspector Instructions:

	<ul style="list-style-type: none"> • Sampling of LCM policies and procedures • Records of LCM laser focus and alignment
	<ul style="list-style-type: none"> • System to positively identify specimens, specimen types and aliquots throughout the process

	
	<ul style="list-style-type: none"> • How is the quality of LCM tissue material ensured?

BAP.06300 Specimen Identification Phase II

There is a system to positively identify all participant specimens, specimen types, and aliquots through all phases of the microdissection and processing procedures to the point of storage or use.

BAP.06400 LCM Procedures Phase II

There is a procedure in place to monitor and document the LCM process.

NOTE: LCM tissues are derivative of a parent block and condition of tissue management is important for the quality outcome of tissue components. This is especially important if the collection is from frozen tissue.

BAP.06500 LCM Equipment Phase II


The LCM Laser focus and alignment is maintained and documented to ensure optimal performance.



NOTE: Documentation related to the critical components of the LCM as noted by the manufacturer is required.

CELL FRACTIONATION

The purpose of cell fractionation is to obtain a pure sample of part of the original whole, such as mitochondria, plasma membranes, DNA, RNA, soluble proteins or even specific macromolecules. There are many procedures defined for each target material, such as tissue, plant cells, animal cells, cell membranes and molecular components. Fractionation can simply be the separation of components of a biospecimen, such as blood into white blood cells, serum, and red blood cells.

Inspector Instructions:

	<ul style="list-style-type: none"> • Sampling of cell fractionation policies and procedures
	<ul style="list-style-type: none"> • System to maintain the identification of the derivatives to the parent biospecimen • Cell fractionation process follows the steps in the procedure

	
	<ul style="list-style-type: none"> How is the quality of the cell fractionation process ensured?

BAP.06600 Specimen Identification Phase II

Derivatives from fractionation of biospecimens maintain the identification associated with the parent biospecimen during the fractionation process.

NOTE: Documentation of specimen type, handling conditions, and, if applicable, storage information are elements of the identification that are maintained until the process is complete. If anonymity from the parent biospecimen is required, this can be accomplished after the fractionation is complete.

BAP.06700 Procedures Phase II

There are written procedures for all steps in the fractionation process.

NOTE: Deviations from the manufacturer instructions must be validated and documented.



BAP.06800 Quality Control/Quality Assurance Phase II

Biorepositories providing cell fractionation procedures must document all quality control and quality assurance measures.

NOTE: These measures would include the establishment of validation sets performed by the laboratory to establish consistent success in quality fractionation and where possible, enrollment in proficiency testing or performance of alternative assessment to demonstrate expertise and quality fractionation.

CELL AND TISSUE CULTURE

Inspector Instructions:

	<ul style="list-style-type: none"> Sampling of cell and tissue culture policies and procedures Sampling of records of microbial contamination and other cell line testing
	<ul style="list-style-type: none"> How does the biorepository ensure that the quality of cell lines is maintained?

****NEW**** 07/29/2013
BAP.06802 **Culturing Environment** **Phase II**

Culturing is performed under aseptic conditions in a biological safety cabinet.

****NEW**** 07/29/2013
BAP.06804 **Cell Line Loss** **Phase I**

There is a system in place to prevent loss of the cell line in case of culture failure, contamination or other problems.

NOTE: Potential systems may include the use of duplicate or independently established cultures, harvesting in duplicate or at different times, or other control processes.

****NEW**** 07/29/2013
BAP.06806 **Monitoring of Passage Numbers** **Phase I**

The biorepository's procedures must define the maximum number of passages for each cell line by either reference or laboratory method.

NOTE: When passages have reached the maximum passage number, the cell line should be re-established using working stock with a lower passage number.

Evidence of Compliance:

- ✓ Documentation of tracking of cell line passages **OR**
- ✓ Documentation of growth curves

****NEW**** 07/29/2013
BAP.06808 **Testing for Microbial Contamination** **Phase I**

Cell lines must be tested for microbial contamination at intervals defined by the biorepository director.

Evidence of Compliance:

- ✓ Records detailing the type(s) of tests and test outcomes

****NEW**** 07/29/2013
BAP.06810 **Testing for Functionality and/or Unique Characteristics** **Phase I**

Cell lines are tested for functionality or unique characteristics.

NOTE: Such testing may be performed by analyzing aspects of the phenotype (e.g. expression patterns), genotype or morphology. The biorepository should have a policy that addresses the need for identity testing.

Evidence of Compliance:

- ✓ Records of cell line evaluation **AND**
- ✓ Records of (short tandem repeats) STR profiling or another method for cell lines to accomplish this goal

****NEW**** 07/29/2013

Culture failures are recorded.

NOTE: Records must indicate corrective actions.





Evidence of Compliance:

- ✓ Documentation indicating the results of testing and indication when a cell line has failed to pass the criteria established for successful passage of the quality tests

HISTOLOGY SECTION

General Quality Control

Inspector Instructions:

	<ul style="list-style-type: none"> • Sampling of specimen preparation records • Sampling of histology QC policies and procedures • Sampling of QC records (histochemical)
	<ul style="list-style-type: none"> • Sampling of tissue blocks (identification) • Sampling of slides (labeling, quality) • Sampling of reagents (expiration date)
	<ul style="list-style-type: none"> • How does the histology section ensure specimen identity throughout processing?
	<ul style="list-style-type: none"> • If problems are identified during the review of histology procedures, further evaluate the responses, corrective actions and resolutions • Select a representative specimen and follow from receipt in the department through accessioning, grossing, processing, time reported and availability in the LIS

****NEW**** 07/29/2013

BAP.06816 Specimen Preparation Records

Phase I

The histology section maintains records of the number of blocks, slides, and stains prepared and appropriately denotes the block from which the slide was prepared.

****NEW**** 07/29/2013

BAP.06818 Reagent Expiration Date

Phase II

All reagents are used within their indicated expiration dates.

NOTE: The biorepository must assign an expiration date to any reagents that do not have a manufacturer-provided expiration date. The assigned expiration date should be based on

known stability, frequency of use, storage conditions, and risk of contamination.

This checklist requirement applies to all reagents used in the biorepository (histochemical, immunohistochemical, and immunofluorescent reagents, and reagents used for molecular tests).

The acceptable performance of histochemical stains is determined by technical assessment on actual case material, use of suitable control sections, and as part of the specimen evaluations as determined by the protocol.

Exception to the above is that some histochemical reagents used in histology are not subject to outdating, so that assignment of expiration dates may have no meaning. The acceptable performance of such reagents should be confirmed at least annually by technical assessment, as described above. (If the manufacturer assigns an expiration date, it must be observed.)

Expired reagents may be used only under the following circumstances, as long as they will not have a negative impact on downstream studies: 1. The reagents are unique, rare or difficult to obtain; or 2. Delivery of new shipments of reagents is delayed through causes not under control of the biorepository. The biorepository must document verification of the performance of expired reagents in accordance with written policy.

If expired reagents are stored in histology, there must be a policy to describe the intended use. The reagents must be stored separately and clearly labeled for the intended purpose (e.g. for training purposes, not for diagnostic use).

Evidence of Compliance:

- ✓ Written policy for evaluating reagents lacking manufacturer's expiration date

REFERENCES

- 1) Department of Health and Human Services, Centers for Medicare and Medicaid Services. Clinical laboratory improvement amendments of 1988; final rule. *Fed Register*. 2003(Jan 24):7164 [42CFR493.1252(c)]

****NEW****

04/21/2014

BAP.06819 Special Stain Quality

Phase II

All histochemical stains are of adequate quality, and daily controls are demonstrated on each day of use for the tissue components or organisms for which they were designed.

NOTE: Positive tissue controls assess the performance of the special stain. Special stains are performed on sections of control tissue known to contain components specific to each special stain. Verification of tissue used as a positive control must be performed and documented before being used with clinical specimens.

Evidence of Compliance:

- ✓ Written procedure for special stains **AND**
- ✓ Records of special stain QC **AND**
- ✓ Documented results of verified special stain control tissue block

REFERENCES

- 1) Department of Health and Human Services, Centers for Medicare and Medicaid Services. Clinical laboratory improvement amendments of 1988; final rule. *Fed Register*. 2003(Jan 24):7166 [42CFR493.1256(e)(2)] and [42CFR493.1273(a)]

****NEW****

07/29/2013

BAP.06820 Special Stains/Studies

Phase II




For special stains and studies using immunologic and FISH/ISH methods, results of controls are documented to be acceptable before reporting results, when applicable.

REFERENCES

- 1) Department of Health and Human Services, Centers for Medicare and Medicaid Services. Clinical laboratory improvement amendments of 1988; final rule. *Fed Register*. 2003(Jan 24):7166 [42CFR493.1256(f)]
- 2) Department of Health and Human Services, Centers for Medicare and Medicaid Services. Clinical laboratory improvement amendments of 1988; final rule. *Fed Register*. 2003(Jan 24):3708 [42CFR493.1256(d)(6)]
- 3) ASCO/CAP ER/PgR guidelines

Immunohistochemistry

Inspector Instructions:

	<ul style="list-style-type: none"> • Sampling of IHC policies and procedures • Sampling of new antibody validation records • Sampling of new reagent/shipment confirmation of acceptability records • Sampling of antibody QC records • Sampling of buffer pH records • Sampling of batch control records
	<ul style="list-style-type: none"> • Sampling of slides (quality)
	<ul style="list-style-type: none"> • How does your biorepository validate new antibodies? • How does your biorepository confirm the acceptability of new reagent lots? • How does your biorepository distinguish non-specific false-positive staining from endogenous biotin?

BAP.06824 Specimen Modification

Phase II

If the biorepository performs immunohistochemical staining on specimens other than formalin-fixed, paraffin-embedded tissue, the written procedure describes appropriate modifications for specimen types.

NOTE: Such specimens include frozen sections, air-dried imprints, cytocentrifuge or other liquid-based preparations, decalcified tissue, and tissues fixed in alcohol blends or other fixatives.

REFERENCES

- 1) Perkins SL, Kjeldsberg CR. Immunophenotyping of lymphomas and leukemias in paraffin-embedded tissues. *Am J Clin Pathol* 1993;99(4):362-373

****NEW** 07/29/2013**

BAP.06826 Buffer pH

Phase II

The pH of the buffers used in immunohistochemistry is routinely monitored.

NOTE: pH must be tested when a new batch is prepared or received.

Evidence of Compliance:

- ✓ Written procedure defining pH range for each buffer in use **AND**
- ✓ Records of initial and subsequent QC on each buffer

Positive tissue controls are used for each antibody.

NOTE: Positive controls assess the performance of the primary antibody. They are performed on sections of tissue known to contain the target antigen, using the same epitope retrieval and immunostaining protocols as the donor tissue. Results of controls must be documented, either in internal biorepository records, or in the donor report. A statement in the report such as, "All controls show appropriate reactivity" is sufficient.

Ideally, the positive control tissue would be the same specimen type as the donor test specimen (e.g. small biopsy, large tissue section, cell block), and would be processed and fixed in the same manner (e.g. formalin-fixed, alcohol-fixed, decalcified) as the donor specimen. However, for most biorepositories, it is not practical to maintain separate positive control samples to cover every possible combination of fixation, processing and specimen type. Thus, it is reasonable for a biorepository to maintain a bank of formalin-fixed tissue samples as its positive controls; these controls can be used for donor specimens that are of different type, or fixed/processed differently, providing that the biorepository can show that these donor specimens exhibit equivalent immunoreactivity. This can be accomplished by parallel testing a small panel of common markers to show that specimens of different type, or processed in a different way (e.g. alcohol-fixed cytology specimens, decalcified tissue) have equivalent immunoreactivity to routinely processed, formalin-fixed tissue.

A separate tissue section may be used as a positive control, but test sections often contain normal elements that express the antigen of interest (internal controls). Internal positive controls are acceptable for these antigens, but the biorepository manual must clearly state the manner in which internal positive controls are used.

A positive control section included on the same slide as the donor tissue is optimal practice because it helps identify failure to apply primary antibody or other critical reagent to the donor test slide; however, one separate positive control per staining run for each antibody in the run (batch control) may be sufficient provided that the control slide is closely scrutinized by a qualified reviewer.

Ideally, positive control tissues possess low levels of antigen expression, as is often seen in neoplasms. Exclusive use of normal tissues that have high levels of antigen expression may result in antibody titers of insufficient sensitivity, leading to false-negative results.

Evidence of Compliance:

- ✓ Written procedure for the selection and use of positive tissue controls for each antibody **AND**
- ✓ Donor reports or worksheet with control results

REFERENCES

- 1) O'Leary TJ. Standardization in immunohistochemistry. *Appl Immunohistochem Molecul Morphol* 2001;9:3-8
- 2) Clinical Laboratory Standards Institute. *Quality Assurance for Design Control and Implementation of Immunohistochemistry Assays; Approved Guideline - Second Edition*. CLSI document I/LA28-A2. Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA; 2011.

Appropriate negative controls are used.

NOTE: Negative controls must assess the presence of nonspecific staining in donor tissue as well as the specificity of each antibody with the exception listed below. Results of controls must be documented, either in internal biorepository records, or in the donor report. A statement in the report such as, "All controls show appropriate reactivity" is

sufficient.

For biorepositories using older biotin-based detection systems, it is important to use a negative reagent control to assess nonspecific or aberrant staining in donor tissue related to the antigen retrieval conditions and/or detection system used. A separate section of donor tissue is processed using the same reagent and epitope retrieval protocol as the donor test slide, except that the primary antibody is omitted, and replaced by any one of the following:

- An unrelated antibody of the same isotype as the primary antibody (for monoclonal primary antibodies)
- An unrelated antibody from the same animal species as the primary antibody (for polyclonal primary antibodies)
- The negative control reagent included in the staining kit
- The diluent/buffer solution in which the primary antibody is diluted

In general, a separate negative reagent control should be run for each block of donor tissue being immunostained; however, for cases in which there is simultaneous staining of multiple blocks from the same specimen with the same antibody (e.g. cytokeratin staining of multiple axillary sentinel lymph nodes), performing a single negative control on one of the blocks may be sufficient provided that all such blocks are fixed and processed identically. This exception does not apply to stains on different types of tissues or those using different antigen retrieval protocols or antibody detection systems. The biorepository director must determine which cases will have only one negative reagent control, and this must be specified in the department's procedure manual.

The negative reagent control would ideally control for each reagent protocol and antibody retrieval condition; however, large antibody panels often employ multiple antigen retrieval procedures. In such cases, a reasonable minimum control would be to perform the negative reagent control using the most aggressive retrieval procedure in the particular antibody panel. Aggressiveness of antigen retrieval (in decreasing order) is as follows: pressure cooker; enzyme digestion; boiling; microwave; steamer; water bath. High pH retrieval should be considered more aggressive than comparable retrieval in citrate buffer at pH 6.0.

Immunohistochemical tests using polymer-based detection systems (biotin-free) are sufficiently free of background reactivity to obviate the need for a negative reagent control and such controls may be omitted at the discretion of the biorepository director, following appropriate validation.

It is also important to assess the specificity of each antibody by a negative tissue control, which must show no staining of tissues known to lack the antigen. The negative tissue control is processed using the same fixation, epitope retrieval and immunostaining protocols as the donor tissue. Unexpected positive staining of such tissues indicates that the test has lost specificity, perhaps because of improper antibody concentration or excessive antigen retrieval. Intrinsic properties of the test tissue may also be the cause of "non-specific" staining. For example, tissues with high endogenous biotin activity such as liver or renal tubules may simulate positive staining when using a detection method based on biotin labeling.

A negative tissue control must be processed for each antibody in a given run. Any of the following can serve as a negative tissue control:

1. Multitissue blocks. These can provide simultaneous positive and negative tissue controls, and are considered "best practice" (see below).
2. The positive control slide or donor test slides, if these slides contain tissue elements that should not react with the antibody.

3. A separate negative tissue control slide.

The type of negative tissue control used (i.e. separate sections, internal controls or multitissue blocks) must be specified in the biorepository manual.

Multitissue blocks may be considered best practice and can have a major role in maintaining quality. When used as a combined positive and negative tissue control as mentioned above, they can serve as a permanent record documenting the sensitivity and specificity of every stain, particularly when mounted on the same slide as the donor tissue. When the components are chosen appropriately, multitissue blocks may be used for many different primary antibodies, decreasing the number of different control blocks needed by the biorepository. Multitissue blocks are also ideal for determining optimal titers of primary antibodies since they allow simultaneous evaluation of many different pieces of tissue. Finally, they are a useful and efficient means to screen new antibodies for sensitivity and specificity or new lots of antibody for consistency, which should be done before putting any antibody into diagnostic use.

Evidence of Compliance:

- ✓ Written procedure for the selection and use of negative reagent (as appropriate) and tissue controls for IHC **AND**
- ✓ Donor reports or worksheet with control results

REFERENCES

- 1) Leong AS-Y, Cooper K, Leong FJW-M. Manual of Diagnostic Antibodies for Immunohistology. 2nd ed. London: Greenwich Medical Media; 2003
- 2) Dabbs DJ, ed. Diagnostic Immunohistochemistry: Theranostic and Genomic Applications. Philadelphia: Saunders/Elsevier; 2010
- 3) Burry RW. Specificity controls for immunocytochemical methods. *J Histochem Cytochem* 2000;48:163-166
- 4) Weirauch M. Multitissue control block for immunohistochemistry. *Lab Med*. 1999;30:448-449
- 5) Miller RT. Multitumor "sandwich" blocks in immunohistochemistry. Simplified method and preparation and practical uses. *Appl Immunohistochem* 1993;1: 156-159
- 6) Chan JKC, Wong CSC, Ku WT, Kwan MY. Reflections on the use of controls in immunohistochemistry and proposal for application of a multitissue spring-roll control block. *Ann Diagn Pathol* 2000;4: 329-336
- 7) Clinical Laboratory Standards Institute. *Quality Assurance for Design Control and Implementation of Immunohistochemistry Assays; Approved Guideline - Second Edition*. CLSI document I/LA28-A2. Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA; 2011.

****NEW****

07/29/2013

BAP.06832 Endogenous Biotin

Phase I

If the biorepository uses an avidin-biotin complex (ABC) detection system (or a related system such as streptavidin-biotin or neutravidin-biotin), there is a policy that addresses nonspecific false-positive staining from endogenous biotin.

NOTE: Biotin is a coenzyme present in mitochondria, and cells that have abundant mitochondria such as hepatocytes, kidney tubules and many tumors (particularly carcinomas) are rich in endogenous biotin. Biotin-rich intranuclear inclusions are also seen in gestational endometrium and in some tumors that form morules. If steps are not included in the immunostaining method to block endogenous biotin before applying the ABC detection complex, nonspecific false-positive staining may occur, particularly when using heat-induced epitope retrieval (which markedly increases the detectability of endogenous biotin). This artifact is often exquisitely localized to tumor cells and may be easily misinterpreted as true immunoreactivity.

Blocking endogenous biotin involves incubating the slides with a solution of free avidin (which binds to endogenous biotin), followed by incubation with a biotin solution (which saturates any empty biotin-binding sites remaining on the avidin). Biotin-blocking steps should be performed immediately after epitope retrieval and before incubation with primary antibody.

REFERENCES

- 1) Miller RT, Kubier P. Blocking of endogenous avidin-binding activity in immunohistochemistry: the use of egg whites. *Appl Immunohistochem* 1997; 5: 63-66

- 2) Miller RT, Kubier P, Reynolds B, Henry T. Blocking of endogenous avidin-binding activity in immunohistochemistry: the use of skim milk as an economical and effective substitute for commercial biotin solutions. *Appl Immunohistochem & Molec Morphol* 1999;7:63-65

****NEW****

07/29/2013

BAP.06834 Control Slide Review

Phase II

The biorepository director or designee reviews all control slides each day specimens are stained.

NOTE: Records of this review must be maintained and should clearly document that positive and negative controls for all antibodies stain appropriately. Control records must be retained for one inspection cycle (every 3 years).

The control slides must be readily available upon request. The location of the slides should be stated in the procedure manual.

REFERENCES

- 1) Shellhorn N. IHC troubleshooting tips. *Advance/Lab.* 2000;9(1):33-37

****NEW****

07/29/2013

BAP.06836 Antibody Validation

Phase II

The biorepository has documented validation of new antibodies, prior to sample characterization, including appropriate positive and negative controls.

NOTE: The performance characteristics of each assay in the immunohistochemistry biorepository must be appropriately validated before being made available as characterization data for the specimen type. The initial goal is to establish the optimal antibody titration, incubation time, temperature, detection system, and antigen retrieval protocol. Once optimized, a panel of tissues must be tested to determine the assay's sensitivity and specificity. The scope of the validation is at the discretion of the biorepository director and will vary with the antibody. For a well-characterized antibody with a limited spectrum of antigenic targets, like chromogranin or prostate specific antigen, the validation can be limited. A panel of 10 positive and 10 negative cases would be sufficient in this setting. For an antibody that is not well characterized and/or has a wide range of reported reactivity, a more extensive validation is necessary. The number of tissues tested should, in this circumstance, be large enough to determine whether the staining profile matches that previously described.

For most antibodies, normal controls are available for use in validation. In the exceptional case where only limited control tissue is available (fewer than 10 cases), the biorepository director should alert the investigator of this limitation.

Evidence of Compliance:

- ✓ Written procedure for the evaluation/validation of new antibodies

REFERENCES

- 1) Hsi ED. A practical approach for evaluating new antibodies in the clinical immunohistochemistry laboratory. *Arch Pathol Lab Med.* 2001;125:289-294
- 2) Clinical Laboratory Standards Institute. *Quality Assurance for Design Control and Implementation of Immunohistochemistry Assays; Approved Guideline - Second Edition.* CLSI document I/LA28-A2. Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA; 2011.

****NEW****

07/29/2013

BAP.06838 New Reagent Lot Confirmation of Acceptability

Phase II

The performance of new lots of antibody and detection system reagents is compared with old lots before or concurrently with being placed into service.

NOTE: Parallel staining is important to control for variables such as disparity in the lots of detection reagents or instrument function. New lots of primary antibody and detection system reagents must be compared to the previous lot using an appropriate panel of control tissues. This comparison must be made on slides cut from the same control block.

Evidence of Compliance:

- ✓ Written procedure for the confirmation of acceptability of new reagent lots prior to use
AND
- ✓ Records of confirmation of new reagent lots

****NEW****

07/29/2013

BAP.06840 Slide Quality

Phase II

The immunohistochemical stains produced are of acceptable technical quality.

NOTE: The biorepository director or designee reviews slides and determines if they are of acceptable technical quality. The inspector must examine examples of the immunohistochemical preparations offered by the biorepository. A reasonable sample might include 5-10 diagnostic antibody panels.

REFERENCES



- 1) Shellhorn N. IHC troubleshooting tips. *Advance/Lab.* 2000;9(1):33-37

Histology Section Safety

NOTE TO THE INSPECTOR: The inspector should review relevant requirements from the Safety section of the General checklist, to assure that the histology section is in compliance.

The following requirements pertain specifically to the histology section.

Inspector Instructions:

	<ul style="list-style-type: none"> • Sampling of histology safety policies and procedures • Sampling of microwave reproducibility and ventilation checks • Sampling of formaldehyde vapor monitoring records
	<ul style="list-style-type: none"> • Location of automated tissue processor • Storage cabinets • Biohazard disposal bins

****NEW****

07/29/2013

BAP.06844 Automated Tissue Processor

Phase II

Each open (i.e. generative of flammable vapors into the ambient workspace) automated tissue processor is operated at least 5 feet from the storage of combustible materials and from the paraffin dispenser.

NOTE: Each open (i.e. generative of flammable vapors into the ambient workspace) automated tissue processor must be located at least 5 feet from the storage of combustible materials unless separated by one-hour fire-resistive construction. Flammable and

combustible liquids must not be positioned near sources of heat or ignition. At least 5 feet must separate each open system tissue processor from the paraffin dispenser.

Tissue processors that operate as a closed system confine ignitable vapor hazards within the processor and thus do not pose a hazard requiring a 1.52 m (5 ft.) separation.

****NEW**** 07/29/2013
BAP.06846 **Microtome Storage** **Phase II**
Microtome knives are stored in original containers or by some other means to avoid personnel injury or equipment damage.

****NEW**** 07/29/2013
BAP.06848 **Waste Disposal** **Phase II**
Infectious tissues and other contaminated materials are disposed of with minimum danger to professional, technical, and custodial personnel.

NOTE: Waste disposal must be in accord with all regulations and disposed of with minimum danger to professional, technical, and custodial personnel.

Evidence of Compliance:

✓ Written procedure for waste disposal in accordance with local regulations

****NEW**** 07/29/2013
BAP.06850 **Creutzfeldt-Jakob Disease (CJD) Special Handling** **Phase II**
There are documented procedures for the special handling of tissues in the biorepository from cases in which Creutzfeldt-Jakob disease is suspected.

NOTE: In addition to specimen handling, the policy should include guidelines for appropriate intralaboratory communication.

Neuropathology tissues from suspected cases of Creutzfeldt-Jakob disease should be treated with formic acid. Paraffin blocks and slides prepared from formic-acid-treated tissue may be handled routinely.

If tissue has not been treated with formic acid, it must be hand-processed and treated as containing potentially transmissible prions. Double gloves must be worn at all times when handling such tissue. All solutions, including water washes, must be collected and treated with equal volumes of fresh undiluted household bleach for 60 minutes before disposal. All scraps of paraffin and unused sections should be collected on a disposable sheet. The microtome may be wiped with bleach or NaOH solution. No special precautions are needed in handling intact glass slides once they have been coverslipped. Broken slides should be decontaminated and discarded. Paraffin blocks should be stored in a bag or box and labeled as infectious. Alternatively, the biorepository may reseal the cut surface of the blocks with paraffin.

NOTE: The following three requirements apply to microwave devices used in the histology section.

****NEW**** 07/29/2013
BAP.06854 **Microwave Usage** **Phase I**
Microwave devices are used in accordance with manufacturer's instructions.

NOTE: Microwave devices should be used in accordance with manufacturer's instructions,

unless CAP requirements are more stringent.

Evidence of Compliance:

- ✓ Written procedure for microwave usage

****NEW****

07/29/2013

BAP.06856 Microwave Monitoring

Phase I

Microwave devices are at least annually monitored for reproducibility.

NOTE: "Reproducibility" is defined as consistency in diagnostic quality obtained from microwave equipment and procedures. For some devices, reproducibility may be evaluated by monitoring the temperatures of identical samples after microwave processing. For those microwave devices (particularly those incorporated into histology processing equipment) that use temperature-independent methods to evaluate reproducibility, the biorepository should have a written procedure for monitoring reproducibility that follows instrument manufacturer's instructions. Information on such procedures is given in the reference to this checklist requirement (see below).

The microwave device should be tested for radiation leakage if there is visible damage to the device.

Evidence of Compliance:

- ✓ Written procedure for monitoring the diagnostic quality of specimens processed using microwaves

REFERENCES

- 1) Clinical and Laboratory Standards Institute. *Microwave Device Use in the Histology Laboratory; Approved Guideline*. CLSI document GP28-A [ISBN 1-56238-563-1]. Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2005

****NEW****

07/29/2013

BAP.06858 Microwave Container Venting

Phase I

All containers used in microwave devices are vented.

NOTE: This checklist item does not apply to microwave devices that are designed by the manufacturer to operate without venting.

Microwave devices should be placed in an appropriate ventilation hood to contain airborne chemical contaminants and potentially infectious agents. Before operation of the microwave device, flammable and corrosive reagents should be removed from the hood, to prevent fire or chemical damage to the electronic components of the device. Microwave devices used outside a fume hood should have an integral fume extractor that is certified by the manufacturer for use in a clinical laboratory.

The effectiveness of ventilation should be monitored at least annually.

This checklist requirement does not apply if only non-hazardous reagents (and non-infectious specimens) are used in the device (e.g. water, certain biological stains, paraffin sections). The biorepository should consult the safety data sheets (formerly MSDS) received with reagents and stains to assist in determining proper handling requirements and safe use.

Venting of containers is necessary so that processing occurs at atmospheric pressure, to prevent explosion. For procedures using pressure above that of the atmosphere, specialized containers must be used, with strict adherence to manufacturer instructions.

Evidence of Compliance:

- ✓ Written procedure for the use of appropriately vented containers **AND**

- ✓ Records of annual evaluation of ventilation effectiveness

****NEW****

07/29/2013

BAP.06860

Formaldehyde/Xylene Safety

Phase II

Formaldehyde and xylene vapor concentrations are maintained below the following maxima, expressed as parts per million, in all areas of the biorepository where formaldehyde or xylene are used.

NOTE: Formaldehyde and xylene vapor concentrations must be monitored in all areas where these reagents are used: e.g. surgical pathology gross dissection room, histology laboratory, etc. Initial monitoring involves identifying all employees who may be exposed at or above the action level or at or above the STEL and accurately determining the exposure of each employee identified. Further formaldehyde monitoring is mandated at least every 6 months if results of the initial monitoring equal or exceed 0.5 ppm (8 hr time-weighted exposure, the "action level") or at least once per year if the results exceed the short term exposure limit (STEL) 2.0 ppm. The laboratory may discontinue periodic formaldehyde monitoring if results from 2 consecutive sampling periods taken at least 7 days apart show that employee exposure is below the action level and the short-term exposure limit, and 1) no change has occurred in production, equipment, process or personnel or control measures that may result in new or additional exposure to formaldehyde, and 2) there have been no reports of conditions that may be associated with formaldehyde exposure.

Formaldehyde monitoring must be repeated any time there is a change in production, equipment, process, personnel, or control measures which may result in new or additional exposure to formaldehyde for any employee involved in the activity. If any personnel report signs or symptoms of respiratory or dermal conditions associated with formaldehyde exposure, the laboratory must promptly monitor the affected person's exposure.

Xylene must be monitored initially, but there is no requirement for periodic monitoring of xylene.

Repeat monitoring should be considered when there is a change in production, equipment, process, personnel, or control measures likely to increase exposure levels.

	8 hr Time-Weighted Exposure Limit	Action Level (8 hr Time-Weighted Exposure)	15 min Short-Term Average Exposure Limit (STEL)
Formaldehyde	0.75	0.5	2.0
Xylene	100		150

Evidence of Compliance:

- ✓ Written procedure for formalin/xylene safety including action limits, criteria for discontinuation of monitoring and criteria for resumption of monitoring **AND**
- ✓ Record of initial formalin/xylene monitoring and repeat monitoring when indicated **AND**
- ✓ Records of corrective action when exposure limits are exceeded




REFERENCES

- 1) Montanaro A. Formaldehyde in the workplace and in the home. Exploring its clinical toxicology. *Lab Med.* 1996;27:752-757
- 2) Goris JA. Minimizing the toxic effects of formaldehyde. *Lab Med.* 1997;29:39-42
- 3) Wenk PA. Disposal of histology stains. *Lab Med.* 1998;29:337-338
- 4) Occupational Safety and Health Administration. 29CFR1910.1048 and 1450, revised July 1, 1998

INSTRUMENTS AND EQUIPMENT

A variety of instruments and equipment are used to support the biorepository. All instruments and equipment should be properly operated, maintained, serviced, and monitored to ensure proper performance. The procedures and schedules for instrument maintenance and function checks must be as thorough and as frequent as specified by the manufacturer. Examples of equipment include, but are not limited to centrifuges, microscopes, incubators, heat blocks, biological safety cabinets, fume hoods, etc.

Inspector Instructions:

	<ul style="list-style-type: none"> • Sampling of instrument policies and procedures • Sampling of instrument maintenance logs and repair records
	<ul style="list-style-type: none"> • Instrument records (promptly retrievable) • Instruments (clean and well-maintained)
	<ul style="list-style-type: none"> • How frequently do you change solutions in the tissue processor? How is the timeframe for changing solutions determined? • How does your laboratory prevent cross-contamination of paraffin sections in the flotation bath? • What do you do when you receive notification of a freezer out of range? • How often do you decontaminate your cryostat?

****NEW**** 04/21/2014

BAP.06880 Instrument/Equipment Function Verification

Phase II

The operation of all instruments and equipment is verified upon installation and after major maintenance and repairs to ensure that they function as intended.

Evidence of Compliance:

- ✓ Written procedure for function verification **AND**
- ✓ Records of function verification

****REVISED**** 04/21/2014

BAP.06900 Maintenance/Function Check Performance

Phase II

Appropriate maintenance and function checks are performed and documented for all instruments (e.g. analyzers) and equipment (e.g. centrifuges) following a defined schedule, at least as frequent as specified by the manufacturer, prior to operation.

NOTE: There must be a schedule and procedure at the instrument/equipment for appropriate function checks and maintenance. These may include (but are not limited to) cleaning, electronic, mechanical and operational checks. The procedure and schedule must be at least as thorough and as frequent as specified by the manufacturer.

Function checks should be designed to detect drift, instability, or malfunction, before the problem is allowed to affect test results.

Since some equipment have no standard frequency or extent for maintenance and function checks, each biorepository should establish a schedule that reasonably reflects the

workload and specifications of its equipment.

BAP.07100 Availability of Instrument and Equipment Service Records Phase II

Instrument and equipment maintenance, function checks, service, and repair records (or copies) are available in a timely manner to, and usable by, the staff operating the equipment.

NOTE: Effective utilization of instruments and equipment by the technical staff depends upon the prompt availability of maintenance, repair, and service documentation (copies are acceptable). Biorepository personnel are responsible for the reliability and proper function of their instruments and must have access to this information. Off-site storage, such as with centralized medical maintenance or computer files, is not precluded if the inspector is satisfied that the records can be promptly retrieved.

****NEW** 04/21/2014 Phase II**
BAP.07110 Automated Stainer

There is a schedule to change the solutions in automated stainers.

NOTE: Solutions must be changed at intervals appropriate for the biorepository's workload. Cleaning of the stainers should be documented when performed.

Evidence of Compliance:

- ✓ Written procedure defining frequency of changing staining solutions **AND**
- ✓ QC records that document compliance with the procedure

****NEW** 07/29/2013 Phase II**
BAP.07120 Incubator QC

Incubators are monitored for temperature, CO₂ level, and humidity on each day of use.

NOTE: The procedure manual must specify the allowable limits for each type of culture. Readings must be recorded each day that cultures are incubated. There must be documentation of corrective action if the allowable limits are exceeded.

Evidence of Compliance:

- ✓ Instrument QC records

BAP.07200 Tissue Processor Solutions Phase II

Solutions are changed as needed.

NOTE: Tissue processor solutions must be changed at intervals appropriate for workload. The settings and solutions of shared processors must be checked before each use.

Evidence of Compliance:

- ✓ Written procedures for a change of solutions based on usage **AND**
- ✓ QC records documented at defined frequency

****NEW** 04/21/2014 Phase II**
BAP.07210 Tissue Processing Programs

Tissue processing programs are validated.

NOTE: To validate new processing programs, the biorepository should run tissue samples of the same size, thickness and fixation in duplicate. Reagents on the processor(s) should be comparable, e.g. all fresh reagents. Process, embed, cut, and stain slides at the same time and evaluate the quality of the blocks, e.g. firmness, ease of cutting. The slides should be evaluated by the pathologist without knowledge of which processing program was used and graded on quality of section and staining. The new processing program must be of equal or better quality before being put into use.

This method may also be used to verify a routine processing program before putting a new processor into production.

Evidence of Compliance:

- ✓ Written procedure for validation of new tissue processing programs **AND**
- ✓ QC records documenting validation

****NEW****

04/21/2014

BAP.07220 Tissue Processing Programs

Phase I

Specific tissue processing programs are available for different types and sizes of specimens.

NOTE: To achieve acceptable results for diagnostic purposes, processing programs may be needed for different sizes and types of specimens. Biopsy specimens may be processed on a shorter schedule than larger specimens; large, dense or fatty specimens and brain specimens will not process adequately on a shorter schedule. A variety of processing programs should be used to achieve good processing results.

Evidence of Compliance:

- ✓ Written procedure defining processing programs for various types and sizes of specimen tissues

BAP.07300 Paraffin Bath and Dispenser Temperature

Phase II

Paraffin baths and dispensers are controlled and maintained.

NOTE:

1. Instruments must be clean and well-maintained
2. The temperature of the dispenser must be correct for the type of paraffin used
3. Temperatures are checked regularly and recorded

The frequency of checks must be determined by the director/designee.

Evidence of Compliance:

- ✓ Documentation of frequency requirements **AND**
- ✓ Records of temperature checks

BAP.07400 Flotation Baths

Phase II

Flotation baths are clean and well-maintained, and there is a procedure for preventing cross-contamination of paraffin sections in the bath.

NOTE: Of particular importance are periodic water changes or blotting of the water surface so that sections from one biospecimen block are not inadvertently carried over to another (so-called "floaters" or "extraneous tissue").

BAP.07500 Microtome Maintenance**Phase I**

Microtomes are clean, well-maintained, properly lubricated, and without excessive play in the advance mechanism.

BAP.07600 Cryostat Decontamination**Phase II**

There is a documented procedure for the decontamination of the cryostat at defined intervals and under defined circumstances, and decontamination records are evident.

NOTE: The cryostat must be defrosted and decontaminated by wiping all exposed surfaces with tuberculocidal disinfectant. The cryostat should be at room temperature during decontamination unless otherwise specified by the manufacturer. This should be done at an interval appropriate for the institution; this must be weekly for instruments used daily. Trimmings and sections for tissue that accumulate inside the cryostat must be removed during decontamination. Although not a requirement, steel mesh gloves should be worn when changing knife blades.




REFERENCES

- 1) Clinical and Laboratory Standards Institute (CLSI). *Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline—Third Edition*. CLSI document M29-A3 (ISBN 1-56238-567-4). Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2005.
- 2) <http://www.well.ox.ac.uk/asset/file/leica-disinfection-2.pdf>
- 3) http://www.epa.gov/oppad001/list_b_tuberculocide.pdf

STORAGE EQUIPMENT

This section of storage equipment for a biorepository should be based on the type of specimen(s) to be stored, the length of time in storage, and the intended use of the specimen(s).

Inspector Instructions:

	<ul style="list-style-type: none"> • Sampling of specimen storage policies and procedures • Sampling of preventative and reactive maintenance procedures • Records of storage container calibrations • Sampling of temperature monitoring records
	<ul style="list-style-type: none"> • Adequate space for storage containers • Active alarm systems in place • Walk-in storage environment • Liquid Nitrogen tanks, if applicable
	<ul style="list-style-type: none"> • What do you do in the event of freezer breakdown? • How do you prevent overflow of storage containers?
	<ul style="list-style-type: none"> • Have you ever suffered a significant loss of samples? How did you address this and what were the corrective/preventative actions that became policy as a result?



BAP.07800 Storage Equipment Calibration/Calibration Verification Phase II

There is a procedure for calibration and calibration verification for all applicable storage equipment.

NOTE: The documentation of calibration and calibration verification includes:

1. *Date calibration was performed*
2. *Identity of person who ran the calibration*
3. *Documentation of results*
4. *Name of the device used against which instrument was calibrated*

Evidence of Compliance:

- ✓ Documentation of calibration/calibration verification **OR** manufacturers' certification of calibration

BAP.07900 Temperature Set Points Phase I

High and low temperature set-points have been established and documented that are appropriate for each storage environment.

NOTE: A best practice is to perform and record temperature mapping for each new freezer prior to being placed in service and periodically for freezers currently in service. The frequency of mapping is determined by the director/designee as well as the review of the data generated.

****REVISED** 07/29/2013**

BAP.08000 Consistent Temperature Phase I

There is evidence that all temperature-controlled storage units maintain the proper temperature throughout the unit.

NOTE: On all temperature-controlled storage units, multiple point temperature readings should be taken on a periodic basis to ensure that a required temperature is maintained throughout. There must be documentation that such readings have been taken. Unrestricted air circulation within the unit reduces the potential for warmer or colder areas that may have detrimental effects on blood/component units without detection by the monitoring system. This requirement also applies to liquid nitrogen (LN2) storage units.

A best practice is to perform and record temperature mapping for each new temperature controlled storage unit prior to being placed in service and periodically for freezers currently in service. The frequency of mapping is determined by the director/designee as well as the review of the data generated.

BAP.08100 Refrigerator/Freezer Temperature QC Phase II

Refrigerator/freezer temperatures are checked and recorded daily.

NOTE: Storage temperature of biospecimens must be appropriate for the type of tissue and its means of preservation. Failure to adhere to requirements could result in a unit not being suitable for the purpose for which it was intended.

This checklist requirement applies to refrigerators/freezers containing reagents or biological specimens. "Daily" means every day (seven days per week, 52 weeks per year). The biorepository must define the acceptable temperature ranges for these units. If temperature(s) are found to be outside of the acceptable range, the biorepository must document appropriate corrective action, which may include evaluation of contents for adverse effects.

The two acceptable ways of recording temperatures are: 1) recording the numerical temperature, or 2) placing a mark on a graph that corresponds to a numerical temperature (either manually, or using a graphical recording device). If the records are manually obtained, the identity of the individual recording the temperature(s) must be documented (recording the initials of the individual is adequate).

The use of automated (including remote) temperature monitoring systems is acceptable, providing that biorepository personnel have ongoing immediate access to the temperature data, so that appropriate corrective action can be taken if a temperature is out of the acceptable range. The functionality of the system must be documented daily.

BAP.08200 Walk-in Storage Criteria Phase II

Walk-in storage systems should have:

- 1. Dual compressors**
- 2. Internal safety release**
- 3. Non-slip floor covering**
- 4. Interior oxygen and CO₂ monitoring system, when required**

BAP.08300 Freezer Preventative Maintenance Phase II

There is a procedure for freezer preventative maintenance.

NOTE: Regular preventive maintenance is required to keep units functioning properly. Routine cleaning and maintenance should be done by assigned employees according to a Preventive Maintenance Schedule. Actions should be targeted at elimination of the causes of equipment failure and unscheduled interruptions. This activity involves regular, routine cleaning, lubricating, testing, calibrating and adjusting, checking for wear and tear and eventually replacing components to avoid breakdown.

Evidence of Compliance:

- ✓ Record of employees trained to perform preventive maintenance **AND**
- ✓ Results of all preventive maintenance will be recorded

BAP.08400 Emergency Response Plan Phase II

There is an emergency response plan if acceptable temperature ranges for refrigerators and/or freezers are exceeded.

BAP.08500 Specimen Transfer Procedure Phase II

There is a procedure for maintaining appropriate temperatures in the event of a system failure.

NOTE: There is a plan in place for transfer and back-up storage. For example, having 10% back-up storage containers would be considered best practices for each type of temperature-controlled unit should any one unit suffer an unrecoverable failure. Failure

mode analysis should be performed to identify possible root causes of failure. Corrective actions should include service calls to providers for system repair, as applicable. Duration of failure should also be recorded, as well as any potential adverse effects to specimens.

Evidence of Compliance:

- ✓ Temperature and alarm records **AND**
- ✓ Updated specimen location records **AND**
- ✓ Corrective action/preventative action documentation

If nitrogen in the liquid phase is used, the following requirements apply.

BAP.08600 Liquid Nitrogen Supplies Phase II

Adequate liquid nitrogen (LN2) supplies are maintained onsite if LN2 is used as refrigerant or coolant for a storage environment.

NOTE: In general, vapor phase storage is the preferred method over storage in the liquid phase of nitrogen because vapor phase provides sufficiently low temperatures to maintain temperatures below the T_g (glass transition temperature). Storage in the vapor stage also avoids safety hazards inherent in liquid phase storage.

****REVISED** 07/29/2013**

BAP.08700 LN2 Monitoring Phase II

LN2 daily usage and LN2 levels are monitored and documented for each storage container.

NOTE: The interval for monitoring of usage must be based on the requirements of the instruments.

Evidence of Compliance:

- ✓ Documentation of usage monitoring, as applicable


BAP.08800 Storage Containers Approval Phase II




All specimen storage containers have been approved for use under intended storage conditions.

NOTE: Refer to contact supplier specification sheet for valid use conditions.

TEMPERATURE MONITORING AND ALARMS

Inspector Instructions:

	<ul style="list-style-type: none"> • Records of traceability to NIST standards • Sampling of temperature logs • Sampling of records of alarm trigger response • Sampling of alarm system testing records
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	<ul style="list-style-type: none"> • Active alarm systems in place • Availability of emergency power supply
	<ul style="list-style-type: none"> • What do you do when a storage container alarm triggers? • What is the biorepository's contingency plan if the alarm system fails? • What do you do if a unit cannot maintain appropriate temperature?
	<ul style="list-style-type: none"> • Select a storage container that has had a temperature failure and follow the process from notification to response and final corrective action

BAP.08900 NIST Thermometer Phase II

An appropriate thermometric standard device of known accuracy (e.g. guaranteed by manufacturer to meet the standards of the National Institute for Standards and Technology) is available.

NOTE: Thermometers should be present on all temperature-controlled instruments and environments and checked daily. Thermometric standard devices should be recalibrated or recertified prior to the date of expiration of the guarantee of calibration; documentation of recalibration/certification should be maintained for review.

BAP.09000 Non-Certified Thermometers Phase II

All non-certified thermometers in use are checked against an appropriate thermometric standard device before initial use.

BAP.09100 Temperature Checks Phase II

Temperatures are checked and recorded on each day of use, specifying the unit and location for all temperature dependent instruments and equipment.

NOTE: Controlled-temperature devices used must have temperatures recorded at least daily for units that are within the prescribed temperature range, and at least every 15 minutes if outside of that range.

The two acceptable ways of recording temperatures are: 1) recording the numerical temperature, or 2) placing a mark on a graph that corresponds to a numerical temperature (either manually, or using a graphical recording device). The identity of the individual recording the temperature(s) must be documented (recording the initials of the individual is adequate).

The use of automated (including remote) temperature monitoring systems is acceptable, providing that biorepository personnel have ongoing immediate access to the temperature data, so that appropriate corrective action can be taken if a temperature is out of the acceptable range. The functionality of the system must be documented daily.

BAP.09200 Alarm Response Time Phase I

Temperature limits for the alarm are established with consideration for anticipated response time.

****REVISED** 07/29/2013**

BAP.09300 Storage Temperature Deviation Procedure Phase II

There are documented procedures to follow if there are deviations in the storage temperature limits, with an impact assessment when required.

NOTE: Specific procedures must be documented and understood by personnel regarding handling biological specimens if storage temperature limits cannot be maintained. The primary concern is the preservation of specimen. If there is a failure, arrangements must be made for service, and for alternative storage.

BAP.09400 Emergency Power Supply Phase II

Temperature controlled storage equipment have an emergency power supply.

BAP.09500 Storage Unit Alarms Phase II

There is an audible alarm for each component storage unit, the alarm is continuously monitored 24 hours per day (in biorepository or remote), and the response system to an alarm has been validated.

NOTE: The biorepository should be able to demonstrate how this system works, and that there is a process to ensure a timely response to an alarm.

Evidence of Compliance:

- ✓ Written procedure defining criteria for monitoring alarms **AND**
- ✓ Records of response time to the alarm

****REVISED** 07/29/2013**

BAP.09600 Alarm System Checks Phase II

Alarm systems functionality is tested (e.g. alarm triggers, ability to communicate, etc.) at specified periodic intervals (no less frequently than quarterly) and results recorded.

NOTE: Freezer alarms should be tested without taking specimens outside their acceptable range. Some ways to perform this testing may include: 1) electronic manipulation of freezer set points to trigger the alarm system, 2) warming or cooling the probe using external measures that do not affect the operating temperature at which the specimens are held, and other acceptable processes.

****REVISED** 07/29/2013**

BAP.09700 Alarm Sensors To Trigger Action Needed Phase II

Alarms are adjusted to be triggered before the temperature falls outside the acceptable temperature range.

NOTE: The biorepository defines the acceptable range for specimen storage.

Evidence of Compliance:

- ✓ Records of trigger temperatures during alarm checks **AND**
- ✓ Records of corrective action, when appropriate

BAP.09800 Power Failure Back-Up Phase II

The alarms will continue to function if the power is interrupted.

NOTE: Alarm systems must continue to function during a power failure. This may be accomplished by having the alarm on a separate circuit, installing battery power back-up, or having a power failure alarm.

BAP.09900 Off-Site Notification Process Phase II

If the monitoring system allows for off-site notification, there is a

- 1. Trained person on-call (24/7) to respond to alarm conditions**
- 2. List of phone numbers or alternate means of contact for trained personnel in case the on-call person fails to respond**

BAP.10000 Back-Up Alarm QC Phase II

There is a back-up alarm system in place with documentation of regular testing.

BAP.10100 Alarm System Monitoring Phase II

There is a mechanism for monitoring the alarm system.

BAP.10200 Alarm System Contingency Plan Phase II

There is a contingency plan in place for monitoring if the alarm system fails.

NOTE: Downtime procedures should exist and staff should be trained on these procedures. This contingency procedure should be periodically tested.



INFORMATION TECHNOLOGY SYSTEMS

If the computer system(s) is located in a remote site, the biorepository should have a service level agreement with the site(s) that states the requirements of the biorepository for data transmission as well as stating the exceptions related to security and other criteria determined necessary by the biorepository.

HARDWARE AND SOFTWARE

Inspector Instructions:

	<ul style="list-style-type: none">• Sampling of hardware and software policies and procedures• Sampling of application training records
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	<ul style="list-style-type: none"> • Sampling of documentation for system modifications • Records of bug-fixes
	<ul style="list-style-type: none"> • How does your biorepository verify the IT system following a hardware or software failure? • Who do you notify when there is a computer malfunction? • Where is the server located? • What are the safety features of the facility or rating where the server is located?

BAP.10300 IT System Testing Phase II

There is documentation that programs are adequately tested for proper functioning after installation of new systems or changes or modification of the existing systems, with documentation of approval for use by the biorepository director or designee.

NOTE: Computer programs must be checked for proper performance after installation of new systems or modifications of existing systems. Any changes or modifications to the system must be documented, and the director or designee must approve all changes, additions and deletions in programs, the test library, and major computer functions before they are released. Documentation must be retained for at least two years beyond the service life of the system.

BAP.10400 Custom IT System Phase II

Customized programs are appropriately documented.

NOTE: The purpose of the computer program, the way it functions, and its interaction with other programs must be clearly stated. The level of detail should be adequate to support trouble-shooting, system modifications, or additional programming.

BAP.10500 Software Bug or Issue Tracking Phase II

There is an adequate tracking system to identify and report all malfunctions or issues with biorepository software.

NOTE: The tracking system should also include responses to reports of software bugs.

Evidence of Compliance:

- ✓ Records of software bugs and issues

BAP.10600 Software Bug or Issue Resolution and Tracking Phase II

There is a written policy for correcting software malfunctions or issues, as well as an audit log of all changes to the software application.

Evidence of Compliance:

- ✓ Audit log of software bugs and issues and corrections made to the system

BAP.10700 Software Modification Tracking Phase II

There is an adequate tracking system to identify all persons who have added or modified software.

Evidence of Compliance:

- ✓ Records of individuals adding or modifying software

BAP.10800 IT System Training Phase II

There is documentation that all users of the computer system receive adequate training initially, after system modification, and after installation of a new system.

BAP.10900 Computer Malfunction Notification Phase II

There is a written policy with instructions for contacting a responsible person (e.g. Computer System Manager) in case of computer malfunction.

Evidence of Compliance:

- ✓ Written policy with instructions for contacting a responsible person in case of system malfunction

BAP.11000 IT System Integrity Phase II

There is a documented process to verify the integrity of the system (operating system, applications, and database) after restoration of data files.

NOTE: The computer system must be checked after restoration of data files to ensure that no inadvertent alterations have occurred that might affect clinical result reporting. The integrity of the system may be verified, for example, by review of a representative number of computer-generated participant reports, or by generating test ("dummy") participant reports for review. The IT director is responsible for determining verification procedure(s) appropriate to the biorepository. Whether or not the data center is located on site, all facilities served by the data center must participate in the verification of the system(s) integrity following a hardware or software failure.


Evidence of Compliance:



- ✓ Records of verification after a hardware or software failure

SYSTEM SECURITY

The following requirements concern unauthorized users. If a system is vulnerable, steps should be taken to prevent unauthorized access.

Inspector Instructions:

	<ul style="list-style-type: none">• Sampling of computer security policies and procedures• Records of system vulnerability tests
	<ul style="list-style-type: none">• Ask a non-IT individual if they have/can install external software on their workstation

	
	<ul style="list-style-type: none"> • Access privileges and restrictions in applications/databases

BAP.11100 Access Data Phase II

There are explicit documented policies that specify who may use the computer system to enter or access data, change data or alter programs.

NOTE: Policies must define those who may only access data and users, who are authorized to enter data, change data, change billing, or alter computer tables or programs.

BAP.11200 Computer Access Codes Phase I

Computer access codes (security codes, user codes) are in place to limit individuals' access to those functions they are authorized to use and the security of access codes is maintained (e.g. inactivated when employees leave, not posted on terminals).

NOTE: The biorepository should establish security (user) codes to permit only specifically authorized individuals to access patient data or alter programs. A system that allows different levels of user access to the system based on the user's authorization is desirable and usually provides effective security. Examples of best practices include these requirements: periodic alteration of passwords by users; minimum character length for passwords; password complexity requirements (e.g. a combination of alphanumeric characters); recording of failed log-on attempts with user lock-out after a defined number of unsuccessful log-on attempts.

BAP.11300 Time-out/Lock-out Phase I

The computer systems have an appropriate security feature such as a mandatory time-out and a password lock-out mechanism.

BAP.11400 System Testing Phase I

Systems are tested in a privileged and non-privileged manner to identify vulnerabilities that may lead to unintentional or unauthorized disclosure and/or modification of data.

Evidence of Compliance:

- ✓ Records and results of vulnerability tests
- ✓ Documented corrective actions if a vulnerability is identified

BAP.11500 Unauthorized Software Installation**Phase I**

Policies and procedures are in place that govern installation of software on any computer used by the biorepository.

NOTE: Biorepository computers often serve multiple functions. Many of these computers are connected in a network. The security of the system should be sufficient to prevent the casual user from installing software. Such unauthorized installation may cause instability of the operating system or introduce other unwanted consequences. Many operating systems allow procedures to restrict certain users from installing software.

BAP.11600 Public Network Security**Phase II**

If the facility uses a public network, such as the Internet (including email) as a data exchange medium, there are adequate network security measures in place to ensure confidentiality of patient data.

NOTE: Information sent over a public domain such as the Internet is considered in the public domain. Thus it is potentially accessible to all parties on that network. Systems must be in place to protect network traffic, such as "fire walls" and data encryption schemes.

Evidence of Compliance:

- ✓ Written policy defining mechanism for data protection

DATA RETRIEVAL AND PRESERVATION

Inspector Instructions:



- Data preservation policies and procedures
- Audit logs detailing users and system changes

BAP.11700 Data/Services Protection**Phase II**

Data and services are protected from loss.

NOTE: Policies and procedures must:

1. *Be adequate to address scheduled and unscheduled interruptions of power or function*
2. *Be tested periodically for effectiveness*
3. *Include systems to backup programs and data*
4. *Include a written plan.*

The performance of the data protection can be performed by in-house staff or by a subcontractor, e.g. documented by a paid invoice.

BAP.11800 Data Input ID**Phase II**

There is an adequate system to identify all individuals who have entered and/or modified data or control files.

NOTE: When data is entered, the system must provide an audit trail to document each

person involved.

REFERENCES

- 1) Jones JB. The importance of integrating POCT data into an organized database. *Advance/Laboratory*. 1999;8(9):8-10
- 2) Halpern NA, Brentjens T. Point of care testing informatics. The critical care-hospital interface. *Crit Care Med*. 1999;15:577-591

BAP.11900 Archived Data

Phase II

Access to archived data, including all data relevant to the biospecimens through the original reports is readily available.

NOTE: Stored data and archival information must be easily and readily retrievable within a time frame consistent with research needs.

BAP.12000 Data Preservation/Destructive Event

Phase II

There are documented procedures for the preservation of data and equipment in case of an unexpected destructive event (e.g. fire, flood), software failure and/or hardware failure, and these procedures allow for the timely restoration of service.



NOTE: These procedures can include (but are not limited to) steps to limit the extent of the destructive event, protocols for periodic backing up and storing of information, procedures for off-site storage of backup data, and protocols/procedures for restoring information from backed up media. The procedures should specifically address the recoverability of participant information. Changes to hardware and software commonly require review and re-evaluation of these documented procedures. These procedures must specifically address the physical environment and equipment. This checklist requirement is often addressed by the organization's disaster plan.

REFERENCES

- 1) Valenstein P, et al. Laboratory computer availability. A College of American Pathologists Q-Probes study of computer downtime in 422 institutions. *Arch Pathol Lab Med*. 1996;120:626-632

INTERFACES

Inspector Instructions:

	<ul style="list-style-type: none">• Interface systems policies and procedures• Sampling of reports transmitted to each interfaced system
	<ul style="list-style-type: none">• How does your facility verify the accuracy of data transmission to interfaced systems?

BAP.12100 Interface Security

Phase II

If data in other computer systems can be accessed through the biorepository system, there are documented policies to prevent unauthorized access to that data.

BAP.12200 Interface Result Integrity**Phase II**

There is a procedure to verify that data are accurately transmitted from the point of data entry to reports (whether paper or electronic).

NOTE: Verification must be performed prior to implementation of an interface (i.e. pre go-live), and every two years thereafter. This includes evaluation of data transmitted to other computer systems and their output devices.

Verification of accurate data transmission to other systems must be performed by reviewing data in the first downstream (or interfaced) system. This requirement can be met by printing screen shots or by other methods that document that a verification procedure has been performed. At implementation of a new interface, or change to an existing interface, validation of at least two examples of reports satisfies the intent of this checklist requirement.

Evidence of Compliance:

- ✓ Records of verification

REFERENCES

- 1) Cowan DF, et al. Validation of the laboratory information system. *Arch Pathol Lab Med.* 1998;122:239-244

BAP.12300 Interface Shutdown/Recovery**Phase II**

There are procedures for changes in processes necessary during partial or complete shutdown and recovery of systems that interface with the information system.




NOTE: These procedures must ensure integrity of data. Procedures must include verifying recovery of interfaced systems, and replacement or updating of data files, as necessary.

REFERENCES

- 1) Valenstein P, et al. Laboratory computer availability. A College of American Pathologists Q-Probes study of computer downtime in 422 institutions. *Arch Pathol Lab Med.* 1996;120:626-632

INVENTORY SYSTEM

Inspector Instructions:

	<ul style="list-style-type: none">• Records of system privilege levels for employees• Records of inventory system audits• Inventory tracking criteria• Sampling of sample distribution records
	<ul style="list-style-type: none">• Sample being removed from inventory• Use of inventory tracking criteria• Sample being placed into inventory• Labeling of specimens with a unique identifier/code
	<ul style="list-style-type: none">• How are privilege levels assigned for the inventory system?• What is the process if a sample entered into the inventory system cannot be located?• What are you looking for when performing a sample pre-distribution quality check?



- Select a specimen in storage and review the audit trail for the specimen
- Is there a system in place to identify the exact refrigerator/freezer where a sample is stored?

BAP.12500 Inventory Process

Phase II

There is a documented inventory management process.

NOTE: Privilege levels should be set for performing specific functions in the system and for access to specific data.

Evidence of Compliance:

- ✓ Documentation of each person's level of access

BAP.12600 Computer-Based Inventory System Privileges

Phase II

If the inventory system is computer-based, the system is controlled by assigning privilege levels to the biorepository staff.

BAP.12700 Computer-Based Inventory System Verification/Audits

Phase II

If a computer-based inventory system is used, it has been verified and is subject to regular quality assurance audits.

NOTE: Frequency of the audits is determined by the director.

****REVISED** 07/29/2013**

BAP.12800 Inventory System Tracking Criteria

Phase II

The inventory system tracks, as applicable:

1. Unique identifier
2. Study and study participant identifier
3. Visit identifier, if applicable
4. Specimen material type
5. Preservatives/additives/preservation methods
6. Specimen *parent/child* relationship, if applicable
7. Specimen vial type
8. Specimen volume
9. Date/time of collection
10. Date/time of receipt into inventory
11. Date/time of processing
12. Date/time and location of distribution
13. Number of thaws
14. Number of times sent previously for testing, if applicable
15. Condition warnings (e.g. partially frozen upon receipt, micro-clots present, frozen sideways, or any other relevant exceptions to the SOP)
16. Clinical data, as applicable
17. Biospecimen status (e.g. reserved or available)
18. Clinical collection site identifier, if applicable

NOTE: If clinical data is not stored at the biorepository in the inventory tracking system,

there is a method for linking the physical spec with the clinical information, as needed.

Information regarding some of these elements may not be available to the biorepository for all biospecimen collections, especially those that were procured before recent best practices for biorepositories were published or for legacy collections.

BAP.12900 Inventory System Audit Trail Criteria Phase II

The inventory system includes a full audit trail of changes made to the database to include:

- 1. Original date**
- 2. Changed date**
- 3. Identity of who made the change**
- 4. Reason for change**
- 5. What was changed**
- 6. How the change was made**

BAP.12950 Specimen Quantity Warnings Phase II

If required by the sponsor, there is a mechanism in place to ensure minimum vial and minimum volume warnings are triggered before quantities fall below collection specified quantities.

NOTE: The warning mechanism may be either manual or automated. The intent of the requirement is inventory based.

BAP.13000 Inventory System Distribution Records Phase II

The inventory system keeps full records for specimens after distribution.

BAP.13100 Environmental Storage Areas Identifiers Phase II

Environmental storage areas (e.g. freezers and refrigerators) have their own unique identifier that includes a defined convention for numbering shelves, racks, boxes, and the location within each container.

BAP.13200 Shipment Acceptance Confirmation Phase II

Recipients are notified before shipping to ensure that appropriate personnel are available to receive the shipment.

BAP.13300 Shipping Tracking Criteria Phase II

Tracking information for shipment of specimens includes the following, as applicable.

- 1. Invoice/tracking number**
- 2. Recipient/source**
- 3. Date of shipment or receipt**
- 4. Courier name and ID# for each package**
- 5. Sample description**

6. Number of samples shipped/received
7. Study name/number
8. Shipping conditions (e.g. dry ice, ambient temperature)
9. Key investigators identification
10. Confirmation of receipt
11. Any discrepancies from manifest and actual shipment
12. Specimen damage

BAP.13400 Specimen/Shipping Manifest Linkage **Phase II**

Specimens are labeled with a unique identifier and/or code.

NOTE: The intent of this requirement is to ensure that specimens arrive with accurate manifest of the contents of the shipping container.

BAP.13500 Reconciliation of Discrepancies **Phase II**

When specimens are retrieved from storage, any discrepancies found are documented and reconciled prior to distribution.

BAP.13600 Pre-Distribution QC **Phase II**

A quality check is performed prior to distribution.


NOTE: Quality checks may include, but are not limited to, gross observations, labeling accuracy, condition of specimens, weight, and verification that storage temperature is appropriate for the shipping temperature.

BAP.13700 Missing Specimen - Inventory Update **Phase II**

If a specimen is missing, inventory is updated to reflect that the specimen cannot be located.

RECORDS AND DISPOSITION

Inspector Instructions:

	<ul style="list-style-type: none"> Policy for record retention Policy for disposition of specimen and data Sampling of disposition records from the last 2 year period
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****NEW** 04/21/2014**
BAP.13740 Record Retention **Phase II**

The biorepository must have a policy that specifies the length of time in which all records, paper and/or electronic, are retained.

NOTE: The length of time will depend on the nature of the record and is determined by the biorepository. The records include, but are not limited to, equipment maintenance and

repair records, clinical and patient information, and records pertaining to closed collections.

BAP.13750 Disposition of Specimens, Data and Regulatory Documents

Phase II

There is a policy consistent with the regulations that govern the biorepository for the disposition of specimens, data, and related regulatory documents.




NOTE: Reasons for disposition may include, but are not limited to:

1. Transfer or termination of collection
2. End of funding period
3. Depletion of the biospecimen
4. Research participant's request for discontinuation
5. Informed consent issues
6. IRB issues
7. Discrepancies between any clinical data and specimens
8. Quality of the physical specimen (e.g. insufficient fixation or processing, hemolysis)

SOURCE FACILITY

If the biorepository is not the source, the requirements under the Source Facility section are not applicable.

Inspector Instructions:

	<ul style="list-style-type: none"> • Sampling of protocol procedures • Sampling of record content when the biorepository is the sponsor • Sampling of source facility procedures • Sampling of collection site audits, when the biorepository is the sponsor
	<ul style="list-style-type: none"> • The QC process for specimens received from collection sites not under the control of the biorepository
	<ul style="list-style-type: none"> • How do you ensure the quality of specimens from collection sites not under the control of the biorepository? • When the biorepository is the collection sponsor, who conducts the audits, how are the audits documented and who ensures corrective action is appropriate when needed?

BAP.13800 Biorepository/Source Facility Responsibilities

Phase II

The responsibilities between the biorepository and the source facility(ies) are clearly documented and available during the inspection, and reviewed by the biorepository within the last 24 months.

BAP.13900 Protocols **Phase II**

There is/are documented protocol(s) describing methods for participant identification, participant education, specimen collection and labeling, specimen preservation, and conditions for transportation, and storage before testing, consistent with good clinical practice and good laboratory practice, when applicable.

NOTE: All specimens must be labeled with a unique identifier and sufficient quality control practices must be in place to ensure appropriate linkage of that identifier to the participant. Protocols may be separate documents or included in the procedure manual.

BAP.13950 Source Facility Procedure Manual **Phase II**

The procedure manual is comprehensive and includes information on the following elements, as applicable to the scope of the biorepository.

- 1. Informed consent**
- 2. Equipment monitoring, calibration, maintenance, and repair**
- 3. Control of biospecimen collection supplies (disposable and reagents)**
- 4. Biospecimen identification and labeling conventions**
- 5. Biospecimen collection and processing methods**
- 6. Storage and retrieval**
- 7. Shipping and receiving**
- 8. Laboratory tests performed in-house including biospecimen QC**
- 9. Biospecimen data collection and management (informatics)**
- 10. Biosafety**
- 11. Training**
- 12. Security**

NOTE: A copy of the procedure manual would enable the sponsor to ensure that best practices are being followed.

BAP.14100 Remote/Collection Sites QC **Phase I**

There is a documented system to monitor the quality of specimens and associated documentation received from remote sites and collection sites not under the control of the biorepository.

BAP.14200 Remote Site Contact Information **Phase I**

Contact information for remote sites should be readily available to personnel at all times to resolve discrepancies or other issues that may arise.

NOTE: This may include active phone numbers, email, etc.

SPONSOR FACILITY

If the biorepository is not the sponsor, the requirements under the Sponsor Facility section are not applicable.

BAP.14220 Registration/License Phase I

If the biorepository is the primary requestor/sponsor for the specimen collection, the biorepository ensures that all source facilities are registered, licensed, and accredited as required by state, and federal regulations, and appropriate for the study.

BAP.14230 Record Content for Sponsor Facility Phase II

If the biorepository is the sponsor for collections, the biorepository keeps a record of the following for each contributing site, as applicable.

1. Principal investigator (PI)
2. Protocol number
3. Protocol title
4. Protocol version date
5. Informed consent
6. Informed consent version date
7. Study expiration date
8. Approval of the above by Institutional Review Board
9. Principal investigator signature for Protocol and version against approval letter
10. Signature and delegation list for employees responsible of consenting patients, sample transport, clinical data, sample processing, manifesting of samples, and coordination of shipments
11. Curriculum vitae of principle investigator
12. License or diploma (for non-US sites) of PI
13. Governmental approval as required for each participating site

BAP.14240 Contributing Sites Audits Phase II

If the biorepository is the sponsor for collections, the regulatory staff at the biorepository performs scheduled audits of contributing sites.

NOTE: The scope of the audit is defined by the activities of the contributing facility. The type of audit (onsite, paper, etc.) and the timeframe are determined by the biorepository.

Evidence of Compliance:




- ✓ Written procedures for auditing external collection sites **AND**
- ✓ Written results of each audit **AND**
- ✓ Corrective action plans for issues of non-compliance and follow up on each plan

INFORMED CONSENT AND INSTITUTIONAL REVIEW BOARD

This section applies to human subjects research only.

Inspector Instructions:

	<ul style="list-style-type: none">• Privacy and confidentiality policies and procedures• Informed consent criteria
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	<ul style="list-style-type: none"> • What action is taken if a sample is received without the proper informed consent documentation? • How do you ensure that the proposed use of human tissue is consistent with the informed consent?
	<ul style="list-style-type: none"> • Select a specimen in storage and review that the proper informed consent documentation is complete

BAP.14600 Informed Consent Criteria Phase II

Mechanisms are in place to ensure that the proposed uses of human tissue with or without data shared for research purposes are consistent with the informed consent and scope of services, when applicable.

NOTE: There are some instances when informed consent and/or waiver of consent are not applicable (e.g. non-human specimens).

Evidence of Compliance:

- ✓ Document outlining the mechanism

BAP.14700 Required Approval(s) Documentation Phase II

When human specimens are to be collected, all of the required approvals (e.g. IRB or other ethics committees) have been documented and appropriate patient consent processes are complete.

NOTE: The only exception to this is when there has been a waiver of consent.

BAP.14800 Informed Consent Documentation Phase II

Informed consent documentation is obtained for the collection, storage, distribution, and use of identifiable human specimens and data.

NOTE: The only exception to this is when there has been a waiver of consent.



BAP.14900 Waiver of Consent Phase II

A waiver of consent, in accordance with applicable laws and/or requirement and approved by the institution's ethics review committee, is obtained when informed consent documentation is not obtained/required.

BAP.15000	Biospecimen/Data Usage	Phase II
	Processes are in place to ensure that the proposed use of the biospecimen/data is within the guidelines of the project and of the informed consent, when applicable.	
BAP.15100	Privacy/Confidentiality	Phase II
	Policies and procedures are in place to ensure the privacy and confidentiality of the patient/donor.	
BAP.15200	Procedures Available for Review	Phase II
	The biorepository's procedures for human specimen collection, processing, storage, and dissemination are available for ethics committee and/or IRB review, as needed.	

DISTRIBUTION POLICIES AND AGREEMENTS

Inspector Instructions:

	<ul style="list-style-type: none"> • Sampling of material transfer agreements (MTAs) • End-user distribution policy
	<ul style="list-style-type: none"> • Who ensures that the MTA includes all the required information? • Describe the MTA process

BAP.15300	Material Transfer Agreements Criteria	Phase II
	Material transfer agreements (MTAs) define the rights and obligations of the provider (biorepository) and recipient (researcher), including allowable uses for the specimen and/or data once transferred.	
BAP.15400	MTA Areas Covered	Phase II
	The MTA addresses each of the following areas as applicable.	
	<ol style="list-style-type: none"> 1. Future distribution of modifications and derivations made by the recipient 2. Documentation of each participant's role in the modifications or derivations 3. Terms of confidentiality 	

BAP.15500 End-User Distribution Policy Criteria

Phase II

The distribution policy includes confirmation that the end-user has IRB approval or there is an MTA in place that provides relevant assurance for the appropriate use of the specimen according to appropriate ethical and legal requirements.

Evidence of Compliance:

✓ Copies of IRB approvals from end-users **OR** copies of MTA agreements

References for Best Practices

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3. *NCI Biospecimen Research Network.* <http://biospecimens.cancer.gov/researchnetwork/>.
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