

NCI Best Practices for Biospecimen Resources

Office of Biorepositories and Biospecimen Research

National Cancer Institute

National Institutes of Health

U.S. Department of Health and Human Services

Table of Contents

INTRODUCTION	1
A. SCOPE, APPLICABILITY, AND IMPLEMENTATION	3
A.1. SCOPE.....	3
A.2. APPLICABILITY AND IMPLEMENTATION.....	3
A.3. FORMAT OF THE NCI BEST PRACTICES	3
B. TECHNICAL AND OPERATIONAL BEST PRACTICES	3
B.1. BIOSPECIMEN RESOURCE MANAGEMENT AND OPERATIONS	4
B.1.1. Organizational Overview of the Biospecimen Resource	4
B.1.2. Biospecimen Resource Personnel	4
B.1.3. Considerations Related to Planning and Development.....	6
B.1.4. Biospecimen Resource Infrastructure and Space Planning.....	7
B.1.5. Overall Operational Considerations	8
B.1.6. Biospecimen Resource Evaluation and Assessment	9
B.2. BIOSPECIMEN COLLECTION, PROCESSING, STORAGE, RETRIEVAL, AND DISSEMINATION... ..	10
B.2.1. Pre-Analytic and Analytic Variables.....	10
B.2.2. Determining Which Biospecimens to Collect.....	11
B.2.3. Defining Reference Ranges	12
B.2.4. Requirement for Evidence-Based Standard Operating Procedures.....	12
B.2.5. Methods Research	12
B.2.6. Biospecimen Storage.....	12
B.2.7. Biospecimen Retrieval	14
B.2.8. Shipping Samples	14
B.3. QUALITY MANAGEMENT	16
B.3.1. Quality Management System	16
B.3.2. Quality Assurance/Quality Control.....	17
B.3.3. Standard Operating Procedures Manual.....	18
B.4. BIOSAFETY	21
B.4.1. Biohazard Precautions.....	21
B.4.2. Biosafety Best Practices	22
B.4.3. General Laboratory Safety	22
B.5. COLLECTING AND MANAGING CLINICAL DATA.....	22
B.5.1. Regulatory Compliance.....	23
B.5.2. Collecting Clinical Data.....	23
B.5.3. Longitudinal Clinical Data.....	23
B.5.4. Informatics to Support the Tracking of Data.....	24
B.6. BIOSPECIMEN RESOURCE INFORMATICS: DATA MANAGEMENT AND INVENTORY CONTROL AND TRACKING	24
B.6.1. Functionality—General.....	25
B.6.2. Functionality—Identification and Tracking of Biospecimens.....	26
B.6.3. Interoperability	27
B.6.4. Development of Biospecimen Resource Informatics Management Systems.....	28

B.6.5. Selection of Biospecimen Resource Informatics Management Systems	28
B.6.6. Validation and Operation of Biospecimen Resource Informatics Systems	29
B.6.7. Regulatory Issues Pertaining to Informatics Systems	29
C. ETHICAL, LEGAL, AND POLICY BEST PRACTICES	30
C.1. PRINCIPLES FOR RESPONSIBLE CUSTODIANSHIP	31
C.1.1. Governance.....	32
C.1.2. Legacy or Contingency Plans.....	32
C.1.3. Policies on Retention.....	32
C.1.4. Conflicts of Interest.....	33
C.1.5. Confidentiality and Security.....	33
C.1.6. Public Communication.....	33
C.2. INFORMED CONSENT	33
C.2.1. Federal Regulations and Guidelines Pertaining to Informed Consent	34
C.2.2. General NCI Recommendations Pertaining to Informed Consent	35
C.2.3. NCI Recommendations on Key Informed Consent Elements and Supplementary Materials	36
C.2.4. Issues Pertaining to Discontinuation of Participation in Research	39
C.2.5. Considerations for Use of Pediatric Biospecimens	40
C.3. PRIVACY AND CONFIDENTIALITY PROTECTIONS	41
C.3.1. Federal Regulations Pertaining to Privacy	41
C.3.2. NCI Recommendations Pertaining to Privacy and Confidentiality	42
C.4. ACCESS TO BIOSPECIMENS AND DATA	43
C.4.1. General Principles for Access Decisions	44
C.4.2. Research Plan	44
C.4.3. Access Policies.....	45
C.4.4. Models of Sustainability.....	45
C.4.5. Availability of Biospecimens	45
C.5. INTELLECTUAL PROPERTY AND RESOURCE SHARING.....	45
C.5.1. Material Transfer Agreements	46
C.5.2. Inventorship.....	47
C.5.3. IP Rights.....	47
C.5.4. Licensing	47
C.5.5. Data and Resource Sharing	47
C.6. CONFLICTS OF INTEREST	47
C.6.1. Investigator Financial COIs	48
C.6.2. Institutional Financial COIs	48
C.6.3. Nonfinancial COIs.....	48
REFERENCES	49
WEB RESOURCES	52
GLOSSARY OF TERMS	57
ACRONYM LIST.....	68

APPENDICES 69

APPENDIX 1. MINIMAL CLINICAL DATA SET 69

APPENDIX 2. ADDITIONAL RESOURCES RELATED TO ETHICAL, LEGAL, AND POLICY ISSUES
IN BIOSPECIMEN RESEARCH 71

APPENDIX 3. GOVERNANCE PLAN..... 75

APPENDIX 4. SAMPLE MATERIAL TRANSFER AGREEMENT 77

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 research in cancer 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. During 2004 and 2005, the NCI first established a transdivisional Biorepository Coordinating Committee and then created the Office of Biorepositories and Biospecimen Research (OBBR) to lead and coordinate a strategic plan to confront and resolve the issues in a stepwise fashion. These efforts culminated with the development of the First-Generation Guidelines for NCI-Supported Biorepositories, a first-iteration document published in the *Federal Register* on April 28, 2006 (71 FR 25184). The Guidelines were subsequently revised based on public comment and input from content experts, renamed the *NCI Best Practices for Biospecimen Resources (NCI Best Practices)*, and released on the OBBR Web site in June 2007.

This revised version of the *NCI Best Practices* is intended to both respond to comments received from the biospecimen resource community and to provide more current and detailed recommendations related to biospecimen and data quality. Major revisions include 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, addition of current references throughout the document, and harmonization with current Federal guidance documents and recommendations from international biospecimen organizations. Like the 2007 release, this version of the *NCI Best Practices* underwent scrutiny by experts within NCI and throughout the National Institutes of Health. It also was posted online for public comment, and the input received was considered as the document was finalized.

The *NCI Best Practices* identifies salient guiding principles that define state-of-the-science biospecimen resource practices, promote biospecimen and data quality, and support 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. 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 biology advances; novel scientific, technological, and clinical practices develop; and new ethical and legal policies and regulations emerge. Results from biospecimen research initiatives will inform future versions of the *NCI Best Practices* as the community moves toward the development of evidence-based 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 resources. 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.

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*

Implementation of the *NCI Best Practices* will be facilitated via an interactive online format that allows users greater flexibility than hard copies in how they access and use the *NCI Best Practices*. In addition, 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*. The interactive format also encourages feedback from the community about the *NCI Best Practices*.

B. Technical and Operational Best Practices

As medicine evolves, researchers are identifying increasing numbers of molecular analytes that characterize both healthy and medical conditions. Careful identification of the presence and levels of such biomarkers can be crucial in diagnostic and treatment decisions. However, mounting evidence indicates that numerous factors in the handling of biospecimens can affect the detection of molecular analytes in downstream analyses (Moore et al. 2011). Although the specific mission of a biospecimen resource will define its collection and processing procedures, common principles apply to all biospecimen types. The technical and operational recommendations in this section have been developed based on current, published information including regulations, guidelines, or established best practices documents in order to promote biospecimen consistency and quality, and to optimize access to such biospecimens and their associated data.

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.

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 [governance structure](#) of the institution.

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. Updated training of personnel should be conducted on a periodic basis, in accordance with applicable regulations and position descriptions (ISBER 2008). 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, 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 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 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 in regard to 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. 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.

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 to promote practices that follow best practice standards.
- Incorporate best practices and current relevant standards into resource policies, SOPs, and procedures with an emphasis on supporting evidence-based practices.

B.1.3.3. Business Planning

Business planning can provide justification for financial and institutional commitment and quantification of startup and sustainability costs.

- 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. 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 and cost-benefit analyses in order to fully assess the inherent intrinsic and extrinsic value. In some cases, a centralized resource model may reduce long-term cost.

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.
- 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.

When possible, biospecimen resources should evaluate options and opportunities for environmentally friendly and/or [Leadership in Energy and Environmental Design](#) (LEED)-certified infrastructure for any and all existing and/or future space.

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 [Specimen Resource Locator](#) ([Section B.6.3](#), Interoperability).

B.1.6. Biospecimen Resource Evaluation and Assessment

The evaluation process can be a valuable exercise to aid executive decisionmaking 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 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 decisionmaking 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.

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.

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 that most closely resemble 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. Such changes may result in inaccurate determinations of the molecular and physical characteristics of those components 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 to be applied when planning biospecimen collection, prior to the initiation of the collection efforts. In addition, study design will dictate whether certain variables 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 variables” and “analytic variables.” Pre-analytic variables refer to factors 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 variables refer to those factors that affect performance of a particular testing procedure.

B.2.1.1. Pre-Analytic Variables

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

- The physiology of the human research participant prior to biospecimen collection;
- Specimen collection practices; and
- Specimen handling practices prior to their inclusion in downstream testing.

B.2.1.1.1. Physiology of the Human Research Participant. Research has demonstrated that levels of analytes may be affected by a variety of factors such as the overall health of the human research participant, food and beverages consumed prior to biospecimen collection, the medication status of the patient, and the time of day at which the biospecimen is collected (Taheri et al. 2004; Rosenkranz et al. 2007). Additional factors, such as phase of the menstrual cycle in females, may affect some downstream analyses. Efforts should be made to collect and record information pertaining to these variables to decrease or adjust for the variability of these contributing factors.

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 (Spruessel et al. 2004; Lin et al. 2006). 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. When biospecimens are collected from participants, the site at which the biospecimen is removed (tumor or nontumor, as well as location within the tumor), any anesthetic being used, the length of time blood flow is blocked from the tissue, 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, and the temperature at which biospecimens are maintained following collection may all affect molecular stability and degradation.

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 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. (ISBER 2008). 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).

B.2.1.1.3. Biospecimen Handling Procedures. Every attempt should be made to optimize the handling of biospecimens to minimize resulting molecular changes that may result from the processing activities. This includes not only the temperature and timing of biospecimen processing but also such considerations as the size and volume of the biospecimen that will be stored for future use. Smaller samples allow for minimal cycles of freezing and thawing. 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 is allowed to proceed.

B.2.1.2. Analytic Variables

When these 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 made:

- Use of validated assays, where possible;
- Standardized training of technical staff in the performance of the assay;
- 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.

B.2.3. Defining Reference Ranges

Aside from pre- and analytic variables, research dictates that values for particular cellular analytes are more accurately represented by a range of values, 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 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 validated 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. Biospecimens that have been poorly handled are likely to provide erroneous test results because of the molecular changes resulting from the handling process.

It is impractical and currently not possible to consider the development of assays to measure every cellular component within a biospecimen. To that effect, protocols that optimize the general stability of biomolecules under certain environmental conditions are recommended (ISBER 2008). 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. Even assays that are developmental in nature should be tested to ensure that they are reproducible over time. “Proof of Performance” tests (ISBER 2008) 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 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.

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 (ISBER 2008; Mager et al. 2004). 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. 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.

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 (Hayes et al. 2002; Holland et al. 2003; Stevens et al. 2007; ISBER 2008). *Paraffin blocks* should be stored at temperatures below 80 °F (27 °C) in an area with pest and humidity control. In the case of *liquids*, such as blood and urine, biospecimen components should be separated before storage to preserve each constituent under its optimal condition. Whole blood (rather than fractional) cryopreservation may be an efficient and cost-effective option for processing viable cells in large-scale studies (Hayes et al. 2002; Stevens et al. 2007). 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 (ISBER 2008). 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.

B.2.6.3.

Storage vessels should be stable under planned storage conditions (Caporaso and Vaught 2002; Saylor et al. 2006; Bell et al. 2010). 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 (Caporaso and Vaught 2002). Snap-frozen biospecimens should be wrapped in aluminum foil or placed in commercial storage containers to minimize desiccation (Bell et al. 2010). 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 (Engel and Moore 2011; Xie et al. 2011). 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 water (Engel and Moore 2011; Xie et al. 2011). Optimal storage conditions might vary according to the final use to which stored sections will be put (Engel and Moore 2011), 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.

B.2.6.5.

Automated security 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 (Landi and Caporaso 1997; Caporaso and Vaught 2002; Eiseman et al. 2003; Friede et al. 2003; ISBER 2008).

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 (Landi and Caporaso 1997; ISBER

2008). 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 (ISBER 2008). 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 (ISBER 2008). Temperature-sensitive material should be handled by a courier with resources to replenish the refrigerant in case of a shipping delay (ISBER 2008). 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 80° F (27° C). 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. Triple packaging should be used for liquid samples. 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](#) 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 (ISBER 2008).

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 (ISBER 2008), 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 (ISBER 2008).

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 (Eiseman et al. 2003).

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 (ISBER 2008; IATA 2009) 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 ([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 (ISBER 2008).

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

- ISBER
<http://www.isber.org>
- Good Laboratory Practices
http://www.oecd.org/document/63/0,2340,en_2649_34381_2346175_1_1_1_1,00.html
- Clinical Laboratory Improvement Amendment
<http://wwwn.cdc.gov/clia/>
- International Organization for Standardization (ISO9000)
<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/cfcr/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.

B.3.3.1. Contents

Specifically, the SOPs manual 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 (Stoneburner et al. 2002). 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.3.3.3. Modifications

Each biospecimen resource should have a document control program and policies for governing, modifying, or revising SOPs. All SOPs should be reviewed at least every 2 years and whenever significant changes in practices, procedures, technology, law, or regulation necessitate an update.

B.3.3.4. Staff Access and Review

Current copies of the SOPs manual should be stored in designated locations and available to the staff at all times. The staff should review new and revised policies and procedures prior to implementation. Staff review and any associated training should be documented.

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 (Grizzle and Fredenburgh 2001). In addition to taking biosafety precautions, biospecimen resources should adhere to key principles of general laboratory safety.

B.4.1. Biohazard Precautions

B.4.1.1.

Laboratories and biospecimen resources should assume that all human specimens are potentially infective and biohazardous (Grizzle and Fredenburgh 2001). For example, OSHA regulations ([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, 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. Additional good general laboratory work practices are outlined by Grizzle and Fredenburgh (2001).

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) (CDC and NIH 2007). 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 ([29 CFR § 1910.1030](#)). Additional precautions should be applied, as outlined in the BMBL. Some activities, such as droplet-based sorting procedures (Schmid et al. 2007), 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 ([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 2008; [29 CFR 1910](#)).

B.5. Collecting and Managing Clinical Data

Appropriate annotation of biospecimens is crucial to the overall usefulness of the biospecimen resource as a tool for scientific research (Eiseman et al. 2003). Biospecimen resources store collected biospecimens using multiple methodologies and procedures. Researchers rely on banked biospecimens for a wide variety of purposes, including target discovery and validation, genetic studies, epidemiologic analyses, and research on prevention or early detection. The data

recorded by investigators and biospecimen resources depend on the types of biospecimens collected and the studies' objectives.

B.5.1. Regulatory Compliance

B.5.1.1.

Data collection activities should conform to U.S. Food and Drug Administration (FDA) requirements (see [21 CFR Part 11](#) or the FDA guidance document at <http://tinyurl.com/21cfr11>), 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.

As appropriate for the purpose and nature of the biospecimen resource, relevant clinical data associated with a biospecimen should be collected in accordance with relevant human subject and privacy regulations. The NCI recognizes that data collection is not necessarily the responsibility of the biospecimen resource.

B.5.2.2.

Biospecimen resources should employ a uniform, nonredundant vocabulary (e.g., Cancer Biomedical Informatics Grid [[caBIG](#)[®]] common data elements [CDEs]) for clinical data.

B.5.2.3.

Biospecimen resources should comply with applicable privacy statutes and regulations and human subjects 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 in compliance, as applicable, with HIPAA, with U.S. Department of Health and Human Services (DHHS) and FDA human subjects protection regulations, and with applicable State and local laws.

B.5.2.4.

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

If the study requirements dictate, biospecimen resources should collect and store longitudinal data following applicable informed consent and authorization requirements.

B.5.3.2.

Depending on the purpose of the biospecimen resource, study design, and/or informed consent/authorization, 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 the Minimal Clinical Data Set, [Appendix 1](#) for a recommended set of 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.5.3.3.

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.

B.5.3.4.

Biospecimen resources should optimize their policies and protocols to facilitate access to uniform longitudinal data (e.g., treatment and outcome information, as appropriate) while protecting research participant privacy and confidentiality.

B.5.3.5.

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. These personnel may not necessarily be employed by the biospecimen resource.

B.5.4. Informatics to Support the Tracking of Data

B.5.4.1.

A biospecimen resource informatics system should track all aspects of biospecimen collection, processing, and distribution to support high-quality annotation of the biospecimen, its characteristics, and other associated data. Refer to [Section B.6](#), Biospecimen Resource Informatics, for additional information.

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

Driven by the scale of data in genomics and proteomics, 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. These informatics systems should be robust and operationally reliable to sustain day-to-day operations of a biospecimen resource and offer the key requirements needed by those

using the biospecimen resource. Informatics systems should be able to adapt and meet changing scientific needs. These needs may include ensuring the system can track new processing methods, new biospecimen protocols, new equipment technology, or new container types.

An informatics system should support all aspects of biospecimen resource operations, including, but not limited to, tracking of research participant enrollment and consent; biospecimen collection, processing, storage, and dissemination; QA/QC processes and documentation; collection of or electronic linkage to research participant (i.e., clinical) data; data security; and management reporting functions (e.g., generating reports on inventory, collection, utilization, QA, etc.). In addition, the system should store a minimum, common set of clinical data.

Biospecimen resource informatics systems are a key tool in providing accountability of biospecimens (e.g., location) and related data uses to research participants. Biospecimen resources should implement and operate their informatics systems with security mechanisms such that this accountability demand is met (see [Section B.6.7](#), Regulatory Issues Pertaining to Informatics Systems, and [Section C.1](#), Principles for Responsible Custodianship).

In addition, the informatics systems should ensure interoperability of systems (i.e., other biospecimen resources or different data systems) because this is key to exchanging data and biospecimens. This should include integrating with other systems where genomic, proteomic, radiology imaging, pathology imaging, and other relevant data are captured or shared.

To address this need, the NCI Center for Bioinformatics developed caBIG. caBIG is a voluntary network grid connecting individuals and institutions to enable the sharing of data and tools across the NCI-supported research continuum, especially for clinical and translational research.¹ Biospecimen resources are encouraged to draw upon caBIG to implement the informatics recommendations in this section. The caBIG program and associated tools/resources enable interoperability for all aspects of cancer research and are continually evolving and growing in scope beyond cancer research. A subset of caBIG tools is available to support biospecimen management and biospecimen sharing.

B.6.1. Functionality—General

B.6.1.1.

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, and distribution from the collection site (research participant) to utilization (researcher).

B.6.1.2.

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.

¹ <https://cabig.nci.nih.gov/>.

B.6.1.3.

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.

Biospecimen resource informatics systems should monitor and report on any recorded measures of biospecimen quality, such as RNA integrity number.

B.6.1.5.

Biospecimen resource informatics systems should provide vital system statistics and audit logs of all access to protected health information (PHI) in the database.

B.6.2. Functionality—Identification and Tracking of Biospecimens

B.6.2.1.

For informatics purposes, a biospecimen refers to a physically distinct human 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 daughter samples, each requiring a new identifier. The origin of each sample should be recorded.

B.6.2.2.

There is a functional need to employ a method to have global unique identification of biospecimens because there are research needs to verify and trace back to the biospecimen original source when 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. Each biospecimen should be assigned a unique identifier or combination of identifiers, such as a number and/or barcode. 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.

B.6.2.3.

The informatics system should be able to track a biospecimen from collection through processing, storage, and distribution. 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 documenting multiple, preexisting, and/or external physical biospecimen identifiers, such as barcodes with nonidentifying information.

B.6.2.4.

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.

B.6.3. Interoperability

B.6.3.1.

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 with other cross-site systems.

B.6.3.2.

The informatics system at each biospecimen resource should be capable of integrating with other clinical data systems, including the anatomic pathology laboratory information system, the clinical pathology laboratory information system, and cancer registries. Integration with clinical data systems should conform to HIPAA regulations and human subjects protection regulations, as applicable.

B.6.3.3.

Informatics systems of biospecimen resources should support a minimum set of common queries that can be submitted to all systems using CDEs.

B.6.3.4.

The informatics systems selected or developed for new biospecimen resources should be caBIG compatible, with the goal of interoperability with other systems.² This will be accomplished by implementing one or more caBIG standard service specifications. The latest information on [caBIG compatibility](#) may be found on the caBIG Web site. Where systems for existing biospecimen resources are being replaced or upgraded, they should be caBIG compatible at a level to ensure maximum available interoperability. For existing software, migration paths to caBIG compatibility should be identified.

B.6.3.5.

The informatics systems should utilize data elements from a common metadata repository, such as the [Cancer Data Standards Repository](#).

B.6.3.6.

Biospecimen resource informatics management systems should be capable of sharing appropriate, deidentified 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 NCI is developing tools for interoperability

² https://cabig.nci.nih.gov/guidelines_documentation.

that aid biospecimen resources in reporting and locating biospecimens, including OBBR and caBIG efforts in the [Specimen Resource Locator](#) and a [caBIG Common Biorepository Model](#) that enables sharing of deidentified biospecimen information via [caGrid](#), an open-source software platform.

B.6.3.7.

Experimental results data from research conducted on biospecimens is typically beyond the scope of information systems used for management of a biospecimen resource. It is therefore not generally realistic to return such data directly to the resource from which biospecimens were obtained. However, submission and storage of experimental data in other systems, including appropriate public data resources, is a best practice for users of biospecimens. When practicable, biospecimen resources should support this practice through interoperability of their informatics systems with the informatics systems used to store experimental data. The use of a global unique identifier is a key best practice for biospecimen resources to achieve this goal ([see B.6.2.2](#)).

B.6.4. Development of Biospecimen Resource Informatics Management Systems

There are a large number of mature, open-source, and commercial informatics system tools that should fulfill the needs of most biospecimen resources. However, these best practices should be considered when opting to develop an informatics management system from scratch.

B.6.4.1.

Biospecimen resource informatics management systems should be based on use cases and other techniques (e.g., data or object models) that capture needs for managing biospecimen resources. SOPs for the activities carried out in a biospecimen resource should largely drive the design of informatics systems.

B.6.4.2.

Software and system development methodology should be followed for initial development and subsequent revisions.

B.6.4.3.

Software and system engineering organizations should be encouraged to meet at least Capability Maturity Model Integration ([CMMI](#)) Level 3.

B.6.5. Selection of Biospecimen Resource Informatics Management Systems

B.6.5.1.

Biospecimen resources should identify the minimum set of requirements for software needs and storage needs to address the current and estimated future needs of the resource. The requirements should incorporate the best practices described in this document.

B.6.5.2.

Biospecimen resources should use criteria identified above to judge mature open-source and commercially available systems, taking into account other factors including ease of implementation, infrastructure needs, support needs, and cost for purchase and maintenance.

B.6.6. Validation and Operation of Biospecimen Resource Informatics Systems

B.6.6.1.

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

B.6.6.2.

Biospecimen resource informatics management systems should have processes defined and in place to cope with system downtimes and disaster recovery.

B.6.6.3.

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.

B.6.6.4.

Tools used to extract structured information from free-text data, such as surgical pathology reports, should be validated to ensure their accuracy in performing that task. Biospecimen resources should have processes in place to routinely monitor the performance of such tools.

B.6.6.5.

All biospecimen resource databases at an individual institution should be in a secure site monitored by the institution. Plans should be in place for data storage and retrieval in response to a wide variety of conditions that could affect the performance of an informatics system. Biospecimen resources should eliminate unsecured, ad hoc databases and manage data through the central informatics system. Resources without the capabilities to provide such infrastructure should seek external hosting arrangements for their informatics system.

B.6.7. Regulatory Issues Pertaining to Informatics Systems

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

B.6.7.1.

Biospecimen resources should meet relevant State and Federal requirements that encourage the use of electronic signatures where appropriate and information technology accessibility standards for handicapped persons.

B.6.7.2.

Biospecimen resources should refer to the National Institute of Standards and Technology Special Publication 800-30 “[Risk Management Guide for Information Technology Systems](#),” as applicable, to determine the appropriate level of security for informatics systems.

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 subjects³), 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 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*. This first revision to the *NCI Best Practices* provides 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 revisions to Section C of the *NCI Best Practices*.

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

³ 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](#).

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](#).

The regulations and proposed standards discussed in this document are for research using biospecimens in the United States. Many countries have their own ethical 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, 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 decisionmaking 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](#) as well as other applicable regulations and policies. (Also see [Section C.6](#), 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](#)) 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. In addition, under DHHS regulations at [45 CFR Part 46 Subpart A](#), 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\(b\)](#) 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 \(d\)](#).

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](#). 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:

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

C.2.1.2.

The OHRP has issued guidance on regulatory requirements that must be satisfied by biospecimen resources (available at <http://www.hhs.gov/ohrp/humansubjects/index.html>). 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.

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](#), [21 CFR Part 50](#), and [21 CFR Part 56](#).) 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.⁴

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 informed consent whenever practicable, consistent with applicable regulations. 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. Some individuals may prefer to provide anonymous samples and/or may be opposed to being recontacted 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.

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 (Andrews 2005; Burhansstipanov et al., 2005). 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.

⁴ 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>.

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 (Hewitt et al. 2009). 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, records 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 anonymized and 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.

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 clinical trials.
- Why particular biospecimens 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 will be used in secondary research.⁵
- Whether biospecimens will continue to be stored 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.

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 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 recontacted about the use of their biospecimens and/or data in future research studies.

⁵ "Secondary research" is defined as any other research use beyond the scope of the primary study.

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. The Genetic Information Nondiscrimination Act ([GINA](#)) 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](#) and the fact sheet produced by the [National Human Genome Research Institute](#).

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, etc. The procedure for opting out of all communications should be clearly indicated. The [HIPAA Privacy Rule](#) may affect the release of research results and should be considered.

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.

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 used 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.2.3.10.

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 OHRP⁶ and [FDA guidance](#).⁷ Participation in research includes the collection of 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

⁶ Guidance on Withdrawal of Subjects from Research: Data Retention and Other Related Issues, released September 21, 2010.

⁷ Guidance for Sponsors, Clinical Investigators, and IRBs: Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials, released October 2008

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](#), 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.⁸ However, the IRB may consider whether a waiver of informed consent under [45 CFR 46.116\(d\)](#) 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.

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 (Eiseman et al. 2003). 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 (Friede et al. 2003). 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 160](#) and Subparts [A](#) and [E](#) of Part 164), was created to protect the privacy of health information that identifies an

⁸ See the OHRP frequently asked questions related to this topic at: <http://answers.hhs.gov/ohrp/categories/1566>.

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 in that human specimens often are accompanied by identifiable protected health information.

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 protected health information (PHI) (see [45 CFR Part 160 and Part 164](#) Subparts A and C). Detailed information on the HIPAA Security Rule is available at <http://www.hhs.gov/ocr/privacy/hipaa/administrative/securityrule/index.html>.

The Health Information Technology for Economic and Clinical Health (HITECH) Act was enacted on February 17, 2009, as Title XIII of Division A and Title IV of Division B of the American Recovery and Reinvestment Act of 2009. Portions of the HITECH Act will impact the provisions and implementation of the HIPAA Privacy Rule and Security Rule. For current information about the HITECH Act as well as detailed information on the HIPAA Privacy Rule, see <http://www.hhs.gov/ocr/privacy>.

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 (Merz et al. 1997). 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 ([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 <http://grants2.nih.gov/grants/policy/coc/index.htm>.

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, and required training for employees. The level of security should be appropriate to the type of biospecimen resource and the sensitivity of the data it houses.

C.3.2.4.

Biospecimen resources should comply with all applicable State and local statutes and regulations pertaining to privacy.

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.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.

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](#) and other applicable [NIH sharing policies](#).

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 at <http://www.hhs.gov/ohrp/policy/hsdc95-02.html>).
- 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](#). 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 <http://www.hhs.gov/ohrp/policy/cdebiol.html>.
- Consistency of the MTA or other appropriate document, as applicable, with the [NIH Research Tools Policy](#) and other applicable [NIH sharing policies](#).
- 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. 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 (for example, see <http://sharing.nih.gov>).

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](#), 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 (for example, see <http://sharing.nih.gov>).

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. 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://ott.od.nih.gov/policy/research_tool.html
- <http://tinyurl.com/AUTM-UMBTA>

- http://grants.nih.gov/grants/policy/data_sharing/
- http://cabig-ut.nci.nih.gov/working_groups/DSIC_SLWG

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](#), other applicable [NIH sharing policies](#), and the [NIH Research Tools Policy](#). 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.

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 § 50, Part F and 45 CFR § 94).⁹ An Investigator is defined by these regulations as the principal investigator and any other person who is responsible for the design,

⁹ NIH is currently in the process of proposed rule-making related to Responsibility of Applicants for Promoting Objectivity in Research for Which Public Health Service Funding Is Sought and Responsible Prospective Contractors. The *NCI Best Practices* will be updated as needed once these regulations are finalized.

conduct, or reporting of research funded by PHS or proposed for such funding. For purposes of the requirements of the regulations, the term Investigator includes the Investigator's spouse and dependent children. 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 § 50.63 and 45 CFR § 94.3, to their institutions. 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](#) 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](#) Web site for more information related to federal employees).

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.

References

- [Andrews LB. Harnessing the benefits of biobanks. *J Law Med Ethics*. 2005;33:22-30.](#)
- [Bell WC, Sexton KC, Grizzle WE. Organizational issues in providing high-quality human tissues and clinical information for the support of biomedical research. *Methods Mol Biol*. 2010;576:1-30.](#)
- [Burhansstipanov L, Bemis L, Kaur JS, Bemis G. Sample genetic policy language for research conducted with native communities. *J Cancer Educ*. 2005;20:52-57.](#)
- Caporaso N, Vaught J. Collection, processing, and analysis of preneoplastic specimens. In: Franco EL, Rohan TE, eds. *Cancer Precursors: Epidemiology, Detection, and Prevention*. New York: Springer-Verlag; 2002.
- CDC (Centers for Disease Control and Prevention) and NIH (National Institutes of Health). *Biosafety in Microbiological and Biomedical Laboratories* [online]. 5th ed. Washington, DC: U.S. Government Printing Office; 2007. Available at <http://www.cdc.gov/od/ohs/biosfty/bmb15/bmb15toc.htm>. Accessed September 1, 2011.
- Eiseman E, Bloom G, Brower J, et al. *Case Studies of Existing Human Tissue Repositories: "Best Practices" for a Biospecimen Resource for the Genomic and Proteomic Era*. Santa Monica, CA: RAND Corporation; 2003.
- [Engel KB, Moore HM. Effects of preanalytical variables on the detection of proteins by immunohistochemistry in formalin-fixed, paraffin-embedded tissue. *Arch Pathol Lab Med*. 2011;135\(5\):537-43.](#)
- Friede A, Grossman R, Hunt R, et al., eds. Biospecimen and data collection and distribution. In: *National Biospecimen Network Blueprint* [online]. Durham, NC: Constella Group, Inc.; 2003. Available at http://biospecimens.cancer.gov/global/pdfs/FINAL_NBN_Blueprint.pdf. Accessed September 1, 2011.
- [Grizzle WE, Fredenburgh J. Avoiding biohazards in medical, veterinary and research laboratories. *Biotechnic & Histochem*. 2001;76:183-206.](#)
- [Hayes RB, Smith CO, Huang WY, et al. Whole blood cryopreservation in epidemiological studies. *Cancer Epidemiol Biomarkers Prev*. 2002;11\(11\):1496-8.](#)
- [Hewitt R, Watson PH, Dhir R, Aamodt R, Thomas G, Mercola D, Grizzle WE, Morente MM. Time of consent for the research use of surgically removed tissue: is postoperative consenting acceptable? *Cancer*. 2009 Jan;115\(1\):4-9.](#)
- [Holland NT, Smith MT, Eskenazi B, et al. Biological sample collection and processing for molecular epidemiological studies. *Mutation Res*. 2003;543:217-34.](#)
- IATA (International Air Transport Association). *Infectious Substances Shipping Guidelines 2009* [online]. 10th ed. Montreal, Canada: International Air Transport Association; 2009. Available for purchase at https://www.iataonline.com/Store/Products/Product+Detail.htm?cs_id=9052-10&cs_catalog=Publications. Accessed September 1, 2011.

[ISBER \(International Society for Biological and Environmental Repositories\). ISBER Best Practices for Repositories: Collection, Storage, Retrieval and Distribution of Biological Materials for Research, Second Edition. *Cell Preserv Technol.* 2008;6:5-58.](#)

Landi MT, Caporaso N. Sample collection, processing, and storage. In: Toniolo P, Boffeta P, Shuker DEG, et al., eds. *Applications of Biomarkers in Cancer Epidemiology*. Lyon, France: International Agency for Research on Cancer; 1997. IARC Scientific Pub. No. 142.

[Lin DW, Coleman IM, Hawley S, et al. Influence of surgical manipulation on prostate gene expression: implications for molecular correlates of treatment effects and disease prognosis. *J Clin Oncol.* 2006;24\(23\):3763-70.](#)

Mager R, Ratcliffe C, Knox K. Developing an operational framework: Standard workflows, operating, and quality control policies and procedures for the collection, storage, and distribution of frozen and paraffin-embedded tissue and blood. Prepared on behalf of DJ Kerr, Director, National Translational Cancer Research Network and National Cancer Research Institute; 2004.

[Merz JF, Sankar P, Taube SE, LiVolsi VA. Use of human tissues in research: clarifying clinician and researcher roles and information flows. *Journal of Investigative Medicine.* 1997;45:252-7.](#)

[Moore HM, Kelly AB, Jewell SD, et al. Biospecimen reporting for improved study quality \(BRISQ\). *J Proteome Res.* 2011;10\(8\):3429-38.](#)

[Rosenkranz RR, Cook CM, Haub MD. Endurance training on low-carbohydrate and grain-based diets: a case study. *Int J Sport Nutr Exerc Metab.* 2007;17\(3\):296-309.](#)

[Saylor DM, McDermott MK, Fuller ER Jr. Analytical model for residual stresses in polymeric containers during cryogenic storage of hematopoietic stem cells. *Acta Biomater.* 2006 Sep;2\(5\):537-46.](#)

[Schmid I, Lambert C, Ambrozak D, et al. International Society for Analytical Cytology biosafety standard for sorting of unfixed cells. *Cytometry A.* 2007;71\(6\):414-37.](#)

[Spruessel A, Steimann G, Jung M, et al. Tissue ischemia time affects gene and protein expression patterns within minutes following surgical tumor excision. *Biotechniques.* 2004;36\(6\):1030-7.](#)

[Stevens VL, Patel AV, Feigelson HS, et al. Cryopreservation of whole blood samples collected in the field for a large epidemiologic study. *Cancer Epidemiol Biomarkers Prev.* 2007 Oct;16\(10\):2160-3.](#)

Stoneburner G, Goguen A, Feringa A. *Risk Management Guide for Information Technology Systems* [online]. Gaithersburg, MD: National Institute of Standards and Technology; 2002. Available at <http://csrc.nist.gov/publications/nistpubs/800-30/sp800-30.pdf>. Accessed September 1, 2011.

[Taheri S, Lin L, Austin D, et al. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. *PLoS Med.* 2004;1\(3\):e62.](#)

[Xie R, Chung JY, Ylaya K, Williams RL, Guerrero N, Nakatsuka N, Badie C, Hewitt SM. Factors influencing the degradation of archival formalin-fixed paraffin-embedded tissue sections. *J Histochem Cytochem.* 2011;59\(4\):356-65.](#)

Web Resources¹⁰

Biological Material Transfer Agreement

Samples and Data for Research: Template for Access Policy Development from the National Cancer Research Institute

http://www.oncoreuk.org/pages/researchers_data.html

Uniform Biological Material Transfer Agreement Federal Register

<http://www.nhlbi.nih.gov/resources/tt/docs/ubmta.pdf>

Code of Federal Regulations

Government Printing Office Access

<http://www.gpoaccess.gov/cfr/index.html>

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/>

¹⁰ All listed Web sites were accessed on August 30, 2011.

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/>

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://www.hhs.gov/ohrp/documents/200811guidance.html>
<http://edocket.access.gpo.gov/2008/pdf/E8-28387.pdf>

Informatics Interoperability

caGrid
<http://cagrid.org/display/cagridhome/Home>

Cancer Data Standards Repository
<https://cabig.nci.nih.gov/concepts/caDSR/>

Specimen Resource Locator
<http://biospecimens.cancer.gov/locator>

Informatics System Development

Capability Maturity Model Integration
Carnegie Mellon[®] Software Engineering Institute
<http://www.sei.cmu.edu/cmml/>

Informatics System Security

Risk Management Guide for Information Technology Systems
National Institute of Standards and Technology
<http://csrc.nist.gov/publications/nistpubs/800-30/sp800-30.pdf>

Laboratory Practices

Clinical Laboratory Improvement Amendment
<http://wwwn.cdc.gov/clia/regs/toc.aspx>

Good Laboratory Practices
http://www.oecd.org/document/63/0,2340,en_2649_34381_2346175_1_1_1_1,00.html

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

Biospecimen Research Network
<http://biospecimens.cancer.gov/researchnetwork/>

cancer Biomedical Informatics Grid[®]
<https://cabig.nci.nih.gov/>

cancer Biomedical Informatics Grid[®] Enterprise Support Network
<http://cabig.nci.nih.gov/esn/>

Data Sharing and Intellectual Capital Workspace
http://cabig-ut.nci.nih.gov/working_groups/DSIC_SLWG

National Biospecimen Network Blueprint
<http://biospecimens.cancer.gov/archive/resources/reports/nbn.asp>

NCI Best Practices Frequently Asked Questions
<http://biospecimens.cancer.gov/practices/faq.asp>

Office of Biorepositories and Biospecimen Research
<http://biospecimens.cancer.gov/>

Symposium-Workshop on Custodianship and Ownership Issues in Biospecimen Research
<http://biospecimens.cancer.gov/archive/resources/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 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://ott.od.nih.gov/policy/research_tool.html

Other Biospecimen Resource References

Case Studies of Existing Human Tissue Repositories—“Best Practices” for a Biospecimen
Resource for the Genomic and Proteomic Era
<http://biospecimens.cancer.gov/archive/resources/reports/csehtr.asp>
<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
<http://www.cancerstaging.org/mission/whatis.html>

Cancer Care Ontario Program in Evidence-Based Care
<http://www.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=10151>

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/StandardsandRegistryOperations/VolumeII.aspx>

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.¹¹ 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, Second Edition* (2008), 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://www.cdc.gov/ncidod/dvrd/spb/mnpages/glossary.htm>).

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).

¹¹ 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/>.

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).

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://www.cdc.gov/ncidod/dvrd/spb/mnpages/glossary.htm>).

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](#)).

cancer Biomedical Informatics Grid (caBIG). A voluntary network or grid connecting individuals and institutions to enable the sharing of data and tools, creating a World Wide Web of cancer research. The goal is to speed the delivery of innovative approaches for the prevention and treatment of cancer. The infrastructure and tools created by caBIG also have broad utility outside the cancer community. caBIG is being developed under the leadership of the National Cancer Institute's Center for Bioinformatics (NCI Thesaurus). For more information, visit <https://cabig.nci.nih.gov>.

cancer Biomedical Informatics Grid (caBIG) compatibility. Refers to meeting caBIG requirements. To aid in the creation of software that will be able to interoperate within the caBIG program, a set of compatibility guidelines was developed that spells out requirements for interoperability in areas of Interface Integration, Vocabularies/Terminologies and Ontologies, Information Models and Data Elements. Systems that meet the requirements are said to be "caBIG compatible."

cancer Data Standards Repository (caDSR). The database that hosts common data elements and information models developed by various NCI-sponsored organizations. caDSR tools facilitate the search and retrieval of common data elements and models. caDSR is the single,

authoritative source of common data (*NCI Best Practices* working definition). For more information, visit <https://cabig.nci.nih.gov/concepts/caDSR/>.

Capability Maturity Model Integration (CMMI). A process improvement approach that provides organizations with the essential elements of effective processes. It can be used to guide process improvement across a project, a division, or an entire organization. CMMI helps integrate traditionally separate organizational functions, set process improvement goals and priorities, provide guidance for quality processes, and provide a point of reference for appraising current processes (Carnegie Mellon[®] Software Engineering Institute CMMI Web site, <http://www.sei.cmu.edu/cmmi/>).

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.gpoaccess.gov/cfr/index.html> 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 (caBIG Glossary, <https://cabig.nci.nih.gov/glossary>).

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](#)). 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,
<http://www.hhs.gov/ohrp/documents/200811guidance.html>).

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 [45 CFR Part 46.107-109](#) 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 (caBIG Glossary, <https://cabig.nci.nih.gov/glossary>).

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://stats.bls.gov/bls/glossary.htm>).

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 ([Babylon Business Dictionary](#)).

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, <http://ttc.nci.nih.gov/>, glossary).

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/ncidod/dhqp/pdf/guidelines/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, <http://ttc.nci.nih.gov/>, glossary). 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
caBIG	Cancer Biomedical Informatics Grid
CDC	Centers for Disease Control and Prevention
CDE	common data element
CMMI	Capability Maturity Model Integration
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
OBRR	Office of Biorepositories and Biospecimen Research
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

National Cancer Institute Best Practices for Biospecimen Resources

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*

National Cancer Institute (NCI) 50-State Survey of Laws Regulating the Collection, Storage, and Use of Human Tissue Specimens and Associated Data for Research

This survey reflects the status of state laws as of November 2004 that affect the use of biospecimens and associated data in research. The report includes a chart with the requirements for the conduct of biospecimen research State by State and a table compiling State statutes.

<http://www.cancerdiagnosis.nci.nih.gov/humanSpecimens/survey/50-state-survey.pdf>

B. *Documents from Other Sources*

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/>

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/PublicPolicy.aspx?id=68>

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.

<http://bioethics.georgetown.edu/nbac/hbm.pdf>

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*

cancer Biomedical Informatics Grid (caBIG)

Members of the caBIG Data Sharing and Intellectual Capital (DSIC) workspace have developed this combined informed consent and Health Insurance Portability and Accountability Act authorization template to facilitate biospecimen and data collection and sharing for research. This is a living document and will be further developed and revised over time.

<https://wiki.nci.nih.gov/display/DSIC/Model+Informed+Consent>

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>

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://www.p3gobservatory.org/repository/ethics.htm>

Sample consent form:

http://www.p3gobservatory.org/download/Modelconsentform_Finalnov6.doc

Sample patient information pamphlet:

http://www.p3gobservatory.org/download/Modelinfosheet_Finalnov6.doc

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/conducting/informed-consent-guide>

Providing Your Tissue for Research

This three-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/publications/posters.php>

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-OHRP-FDA Initiative

The NCI, along with the OHRP and the U.S. Food and Drug Administration, formed an Informed Consent Working Group to address concerns that informed consent documents for clinical trials were becoming too long, complicated, and difficult to understand. In 1998, the group issued “Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials.” The recommendations may be used by investigators developing consent documents and by IRBs reviewing such documents.

<http://www.cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/>

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>

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.

http://www.centerforhealthstudies.org/capabilities/readability/readability_home.html

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 (http://ott.od.nih.gov/policy/research_tool.html).
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.

SIGNATURES APPEAR ON THE FOLLOWING PAGE

Signatures for Provider

Provider Scientist:
Provider Organization:
Address:

Name of Authorized Official:
Title of Authorized Official:

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

Recipient Scientist:
Recipient Organization:
Address:

Name of Authorized Official:
Title of Authorized Official:

Signature of Authorized Official Date

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

Scientist Receiving Material Date