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NCI Best Practices for Biospecimen Resources

Biorepositories and Biospecimen Research Branch

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INTRODUCTION

Biospecimens are a direct source of the molecular data from which targets for therapy, detection, and prevention are identified and molecular taxonomies of cancer are derived. Human specimens are therefore a critical resource for basic and translational cancer research. A pressing need for research biospecimens has arisen in recent years, driven in part by advances in biotechnology that have greatly increased the power and precision of analytical tools used in cancer research and enabled a new era of precision medicine. The reliability and reproducibility of the derived molecular data can be highly dependent on the methodology and consistency with which the biospecimens under study were collected, processed, and stored, as well as the quality of any associated data.

Recognizing that variation in biospecimen collection, processing, and storage procedures could be a major contributing factor to the problem of research reproducibility, the National Cancer Institute (NCI) began in the mid-2000's an intensive due diligence process to understand the state of its funded biospecimen resources and the quality of biospecimens used in cancer research. This process culminated with the development of the *NCI Best Practices for Biospecimen Resources ("NCI Best Practices")*[1], which was accepted by the National Cancer Advisory Board and first published in 2007. The *NCI Best Practices* identifies salient guiding principles that define state-of-the-science biospecimen resource practices, promotes biospecimen and data quality, and supports adherence to ethical and regulatory requirements. The *NCI Best Practices* does not comprise detailed laboratory procedures; rather, the document outlines principles by which such procedures should be developed by biospecimen resources.

The first revision to the *NCI Best Practices* in 2011 provided additional recommendations for best practices concerning the custodianship of biospecimens and associated data; introduced new sections on biospecimen resource management and operations and conflicts of interest (COIs); and aligned the document with current Federal guidance and recommendations from international biospecimen organizations [2]. In the 2016 revision, the *Ethical, Legal, and Policy Best Practices* were updated based on evolving guidance concerning informed consent, return of individual results and incidental findings, and community engagement [3]. The 2016 revision also provided updated Technical and Operational recommendations based on more recent research, guidance, and standards for collecting, processing, and storing specimens.

The 2026 revision of the *NCI Best Practices* brings significant updates, including the reordering and reorganizing of sections of the document. A new, overarching *Governance* section replaces and expands upon the previous *Ethical, Legal, and Policy Best Practices* section. With this, we "begin at the beginning" [4] of the process of creating a biospecimen resource, reflecting the fact that any biospecimen collection is fundamentally guided at its outset by ethical, regulatory, and operational principles that must be adopted, developed, and managed on an ongoing basis. The *Governance* section emphasizes the role of research participants as partners and the fiduciary duty of the custodians of biospecimen resources to protect sample integrity and maintain the confidentiality of identifiable data.

Major updates to the 2026 version include discussion of regulatory changes imposed by implementation of the 2018 Common Rule "Final Rule" requirements, updating Department of Health and Human Services (DHHS) regulations protecting human research subjects at 45 Code of Federal Regulations (CFR) part 46. This update also includes new recommendations that address evolving norms and consensus regarding the management of risks associated with genomic and other molecular-based technologies, ethical and operational considerations regarding the sharing of study findings and clinically actionable individual results, and the importance of community engagement. An expanded section on legacy planning is also included. The 2026 revision also includes extensive updates on biospecimen collection, processing, storage, retrieval, and distribution, along with updated content on biospecimen science and biospecimen evidence-based best practices, with supporting references. Courtesy of the College of American Pathologists (CAP), an updated CAP BAP (Biorepository Accreditation Program) checklist is also provided for reference (see Appendix 6). Updated references, web resources, and additional appendices are also provided in the current version.

Best practices for biospecimen resources have continued to evolve internationally as the field of biospecimen science advances and the research community moves toward the development and utilization of evidence-based practices [5-9]. This evolution is further driven by the development of novel scientific, technological, and clinical practices; the emergence of new ethical and legal policies and regulations; and a growing shift in biobanking strategies toward fit-for-purpose biospecimens and associated data. Additional best practices efforts have been launched and include the comprehensive best practices published by the International Society for Biological and Environmental Repositories (ISBER) [10]. Many of the principles outlined in the NCI and ISBER Best Practices have been adopted, in whole or in part, by accreditation programs for biorepositories, such as the Biorepository Accreditation Program (BAP) of the College of American Pathologists (College of American Pathologists, or CAP) [11], the American National Standards Institute (ANSI) National Accreditation Board (ANAB) Biobanking Accreditation Program [12], and the International Standards Organization [13]. Organizations contemplating an application for accreditation by CAP or other entities will find careful review of the *NCI Best Practices* a helpful starting point in evaluating biospecimen resource practices and administrative oversight.

The recommendations contained within this document are intended to be adapted, as appropriate, based on the mission and scientific needs of individual biospecimen resources. Although adoption of the *NCI Best Practices* is voluntary, biospecimen resources are encouraged to align with the principles outlined in this document and take a leading role in optimizing biospecimens for cancer research and improving research reproducibility.

NATIONAL CANCER INSTITUTE
BEST PRACTICES FOR BIOSPECIMEN RESOURCES

A. Scope, Applicability, and Implementation

A.1. Scope

This document identifies high-level biospecimen best practices that may be utilized to improve the level of consistency and standardization across biospecimen resources[1]. A "biospecimen resource" is defined as a collection of human specimens and associated data for research purposes, the physical structure where the collection is stored, and all associated processes and policies. Biospecimen resources vary considerably, ranging from formal organizations to informal collections of materials in an individual researcher's freezer. The scope of this document includes best practices for biospecimen resource governance (which encompasses ethical, legal, and policy best practices) along with technical and operational best practices.

Best Practices for postmortem recovery of human specimens are addressed in a separate document, *Best Practices for Postmortem Recovery of Normal Human Tissue for Research* (see [14]).

NCI Biospecimen Evidence-based Best Practices, procedural guidelines with literature annotation, are also available online [5]. See also Section C.2.6. Role of Evidence-Based Standard Operating Procedures.

A.2. Applicability and Implementation

The *NCI Best Practices* are intended to be applicable to all types of biospecimen resources that manage human specimens. The implementation of the *NCI Best Practices* is voluntary, and several recommendations can be broadly or narrowly applied depending on the mission and goals of the biospecimen resource and/or the specific study design. Biospecimen resource managers are encouraged to implement the *NCI Best Practices* within their biospecimen management plans, as appropriate.

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

This online version of the *NCI Best Practices* includes additional resources, tools, and references to assist the biospecimen resource community in the effective implementation of the *NCI Best Practices*.

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

B. Governance

B.1. Overview

The *NCI Best Practices* begins with a discussion of governance, with the rationale that any collection of human biospecimens is guided by ethical, regulatory, and operational principles that are adopted, planned, and managed on an ongoing basis. A governance plan is the principled framework for a biospecimen resource that outlines the scientific objectives of the resource; the study protocol(s) or other documents defining the policies for participant recruitment; the biospecimen and data collection plans of the resource; the potential research use of the biospecimens and data; the data management and sharing plan(s); dissemination of study findings; and, as appropriate, policies and recommendations regarding the return of results to research participants[2]. Governance plans also include appropriate protections for the physical integrity of biospecimens and data as well as procedures for the dissemination and use of the resource based on ethical, regulatory, and study principles. Governance plans require careful planning and transparent policies to ensure the long-term physical quality of biospecimens and the integrity of associated data, the privacy of research participants, the confidentiality of associated data, and the ethical, appropriate, and permitted uses of biospecimens and data. Plans for the intended use of the resource should be transparent and align with the information in the informed consent provided to participants.

Different stakeholders may have an interest and a role in establishing the governance plan. These may include, for example, the sponsor, the institution, the institutional review board (IRB), the investigators, health care providers, researchers, patient advocates, research participants, and members of the research participants' communities (see Section B.3. Engagement of Patients, Providers, and Communities). Individual stakeholders should be free of any conflict of interest.

The governance plan should be developed during the planning phase before recruitment and biospecimen collection begin and should address the formal and continuing responsibilities of the stakeholders. For example, policies and decisions regarding dissemination of biospecimens and data should be developed early in the design process and may take considerable time, thought, and preparation while plans are being made for the biospecimen collection phase. The governance plan should be continually assessed over the course of the collection phase, and beyond, for suitability, risks, and potential improvements to effectively support and manage the biospecimen resource as technologies are developed and as ethical, regulatory, and operational policies change and evolve. Governance principles that apply to formally established biospecimen resources are also relevant to the collection, storage, distribution, and use of biospecimens in small collections held by individual investigators. Research investigators with small biospecimen collections intended for future studies may consider joining an institutional biospecimen resource, when available, to help ensure that baseline quality standards are met.

A governance plan should address each of these issues and responsibilities:

- Adherence to Federal, State, and local laws and regulations governing the collection, storage, dissemination, and use of biospecimens and data (see Section B.7. Privacy and Confidentiality Protections).
- Biospecimen storage and archival practices that maximize utility for analysis, data sharing, and research uses of biospecimens (see Section B.8. Access to Biospecimens and Data).

[2] The term "research participants" refers to the persons who have consented to a research study and/or biobanking of their specimens and data. Except when discussing or citing federal regulations, the *NCI Best Practices* uses the phrase "research participant" or "participant," in lieu of the regulatory language "human subject(s)," to recognize the important and active role of patients and volunteers in research. "Research participant" is intended to have the same meaning as human subject, as defined in 45 CFR Part 46.

- Appropriate protections for the physical integrity of biospecimens and data with associated plans and safeguards (see Section B.12. Legacy and Contingency Plans).
- Plans for strategic data collection, aligned with scientific objectives, to ensure the usefulness of the associated annotation for downstream researchers (see Sections B.8. Access to Biospecimens and Data and B.11. Biobank Sustainability).
- Plans for the ethical and fair-minded distribution of samples and associated data to investigators for scientifically meritorious studies (Also see Section B.8. Access to Biospecimens and Data).
- Protections for the confidentiality of collected data and the privacy of biospecimen contributors (see Section B.7. Privacy and Confidentiality Protections).
- Consideration of the needs, goals, and preferences of the affected research participants, and how these will be ascertained and included in governance plans (see Section B.5. Informed Consent).
- Plans to establish and maintain trustworthiness with individual biospecimen contributors, the community groups they represent, with researchers, and the general public (see Section B.3. Engagement of Patients, Providers, and Communities) [15-18].
- Plans for facilitating the unbiased collection of biospecimens from people who reflect the makeup of communities that will benefit from the research (see Section B.3. Engagement of Patients, Providers, and Communities).
- Steps to minimize individual and group harms (see Section B.7. Privacy and Confidentiality Protections).
- Roles and responsibilities of stakeholders involved in all aspects of developing and managing the biospecimen resource (see Section B.2. Roles, Responsibilities and Ownership.
- Proactive legacy planning, especially for resources with term-limited funding, outlining scenarios for the disposition of biospecimens and data in the event of financial insolvency or discontinuation (see Section B.12. Legacy and Contingency Plans).

Specific attention should be given to determining relevant and useful data elements about the biospecimens and the research participants who provided them (e.g., clinical, pathological, or demographic data) [19-23]. The primary intended uses of the biospecimens and data, as well as any potential future unspecified use, should be considered when identifying data elements to record and the process and mechanism for collecting and storing them. The mechanisms or platforms for sharing biospecimens and data, such as an online catalog and/or data repository, and their access policies, must be considered to ensure, in advance, that informed consent documents accurately reflect those plans.

Indeed, all aspects regarding the collection, maintenance, protection, sharing, and ultimate disposition of biospecimens and associated data should be guided by the biospecimen resource's policies and procedures as outlined in their governance plan.

B.2. Roles, Responsibilities and Ownership

As outlined above, different stakeholders may have an interest and a role in establishing the governance plan for a biospecimen resource. The stakeholders may include, but are not limited to, the sponsor, the institution, the IRB, the investigator, and the research participants who contributed the biospecimens as well as the communities that they represent (see Section B.3. Engagement of Patients, Providers, and Communities). The key conceptual categories of custodian and steward may be helpful in defining roles and responsibilities.

The custodian is the trusted caretaker of the resource who provides appropriate protections for the physical integrity of biospecimens and data [24]. The steward of the resource is responsible for the development, implementation, and oversight of fair and ethical policies and procedures for the dissemination and use of the resource. Custodianship and stewardship require careful planning and transparent policies to ensure the long-term physical quality of the biospecimens and the integrity of associated data, the privacy of research participants, the confidentiality of associated data, and the ethical, appropriate, permitted uses of biospecimens and data. The stewardship plans should also address the appropriate return of individual research results or incidental findings where applicable (see Section B.6. Return of Results). The plans for stewardship regarding use of the resource should be transparent to the public and align with the information in the informed consent provided to research participants.

There is significant commonality between the roles and responsibilities of a custodian and a steward, and in some circumstances, the roles may be filled by the same person, entity, or institution. Regardless, the responsibility for stewardship should be clearly designated, and, whether the steward is an individual or a committee, they must be free of conflicts of interest.

Ownership of biospecimens is a complex concept for biospecimen resources. Notably, there is little legal precedent regarding the ownership of biospecimens and data contributed for research, although the few existing cases [25-29] reflect the consensus that the institution where the resource resides is generally considered the owner. However, ethical and societal concepts of biospecimen ownership continue to evolve, with some arguing that the biospecimen donor has ownership rights and, in fact, should be able to profit from donating their tissue [30]. Biospecimen resources may wish to be aware of the evolving nature of the ownership concept as they develop governance policies and manage them over time [31, 32]. In addition, contemporary biobank models are increasingly emphasizing the role of participants as partners, suggesting a shift from traditional ownership models toward models based on rights, reciprocity, and shared benefits. Ultimately, biospecimen resources may consider that, in any case, they are the custodians, if not the legal owners, of the biospecimens in their charge [24].

B.3. Engagement of Stakeholder Communities

Community engagement, the process of involving community stakeholders in biospecimen resource governance and oversight, is an increasingly important component of biospecimen resource governance. Authentic community engagement is an ethical imperative in research biobanking and is essential to engender trust with stakeholders. Community stakeholders may be individuals or groups who are responsible for, or affected by, biobanking research activities (see [33]). Stakeholders may include patients, their families and community members, caregivers, patient advocates, healthcare providers, and researchers who may conduct scientific research with the samples. Fostering participation through community engagement requires collaborating with stakeholders in the planning and operations of the biospecimen resource and, when possible, maintaining ongoing relationships with the community.

Scientific advances depend on the existence of research biobanks and databases that appropriately reflect the broad makeup of the communities that will benefit from the research. Engagement of patients and their families and communities may increase research participation and help ensure that research results are broadly applicable [34]. Developing trust and trustworthiness among patient communities is critical and may require focused effort to communicate the trustworthiness of the investigators and institutions, rather than relying solely on consent processes or informational materials. The concept of research leaders working to establish trustworthiness with research participants and their communities has been discussed in the literature [15, 17, 18].

There is no single approach to community engagement that is adaptable to all biospecimen resources involved in conducting research. Determining appropriate community engagement methods will depend upon the size and institutional framework of the biospecimen resource, available funding and expertise, and the nature and scope of the sample and data collections [35, 36]. For some activities of a biospecimen resource, stakeholder engagement may be considered less critical, for example, for the use of archived biospecimens or for minimal-risk research [37]. Regulatory limitations, particularly for government and non-profit institutions, must also be considered.

Biobanking governance topics that may be brought to stakeholders for their guidance and input include, but are not limited to:

1. Informed consent content, practice, and process.
2. Privacy and security measures for biospecimens and associated data.
3. Legacy and contingency plans related to retention, transfer, or destruction of biospecimens.
4. Transparency, trust, and communication strategies.
5. Stewardship policies related to access to biospecimens and data.
6. Return of individual results and provision of lay summaries of research progress and findings.
7. Policies for publication and other dissemination of research results.

Community engagement activities may range from public forums to the inclusion of patient advocates or community representatives on access or governance committees. Strategies for community engagement in biobanking may include but are not limited to: (i) deliberative community engagement [38, 39], which can involve education and capacity building as well as facilitated discussion amongst stakeholders that may be followed by a democratic voting process for governance and oversight of the biospecimen resource; (ii) community forums, town hall meetings and focus groups [40]; (iii) consultations with group/tribal/spiritual representatives; (iii) community advisory boards comprised of volunteers who meet on a periodic basis to set or review operational and management policies [41]; (iv) public education and feedback solicitation via a public website or an alternate broad communication strategy (All of Us, [36, 42]; Cancer Moonshot Biobank, [43]); (v) key informant in-depth qualitative interviews with individuals having direct knowledge or experience about a particular topic; (vi) surveys and questionnaires; and (vii) inclusion of stakeholders in some or all planning and governance activities, including study design. Each of these engagement strategies [44-46]

ideally will treat communities as partners in the research and promote the underlying ethical values of individual and group autonomy, transparency, and accountability. As part of biospecimen resource planning activities, input from the affected community may be sought regarding the perceived risk-benefit ratio of the proposed research. For example, comments obtained during community engagement may guide decisions regarding consent requirements for the continued use of identifiable pediatric specimens when participants reach the age of majority [47].

In general, the following recommendations may be considered when engaging the stakeholder community:

- Start the community engagement process early, ideally while drafting the governance plan (for example, see [38]).
- Identify all relevant community(s) and stakeholders, including but not limited to patients, patient advocates, families, caregivers, healthcare providers, and researchers who may utilize the samples.
- View community engagement as a continuous and longitudinal process, ideally beginning in the planning stages of the biospecimen resource and extending throughout and after study completion (for example, see [48]).
- Prioritize community input when research dissemination may risk stigmatization or discrimination of specific groups (for example, see [49]).
- Foster effective, longitudinal, and bidirectional communication (for example, see [50]).
- Maintain transparency and accountability with prospective participants and amongst stakeholders [50, 51].

B.4. Transparency and Communication

Transparency, openness, and clear and respectful communication between biospecimen resources and those who contribute samples and data are paramount to the establishment and maintenance of trust. Communication systems should be bidirectional and continual, offering opportunities for biospecimen contributors to ask questions, provide input, and receive updates about the use of their specimens and data. Materials intended for communication with the public and with research participants should ideally be written in plain language and at an appropriate grade level using published health literacy principles [52, 53]; such materials should ideally be readily available and, if applicable, posted online at the resource's or institution's Website.

Biospecimen resources should publicly describe their governance plan, or plans in the case of multiple collections, and organizational structure and provide the following general information via their website or other easily accessible format, such as a printed brochure:

- The entity or entities that fund(s) the biospecimen resource.
- The mission, goals, purpose, and/or scientific objective of the resource.
- Whether biospecimens and data are to be shared with non-profit and/or for-profit researchers.
- How access decisions are made, including the criteria for review and approval, and what privacy protections are in place for biospecimens and identifiable data.
- The types of research studies that may be performed using biospecimens and data.
- If and when available, informed consent templates for research studies using samples and data from the biospecimen resource.
- Whether the biospecimen resource intends to disclose aggregated, de-identified study findings to the public or research participants.

- Whether the biospecimen resource supports research studies that intend to disclose individual results and/or incidental findings.
- General information about conflict of interest (COI), institutional policies for sharing samples with other investigators or companies, the financial implications of sharing, and any known or foreseeable benefit to the institution, the investigator, or commercial partners (Also see Section B.10. Conflict of Interest (COI)).
- Contact information for biospecimen resource management/leadership.

B.5. Informed Consent

Informed consent in research and biobanking encompasses more than a form to be signed; it includes the entire process of ethically recruiting, adequately informing potential research participants, and providing any necessary follow-up communications. Informed consent pursuant to the DHHS human subjects' regulations at 45 CFR Part 46 Subpart A [54] is designed to present potential research participants with sufficient information—including anticipated procedures, risks, and benefits—to make an informed decision about whether to participate in research studies. Ideally, potential participants are also informed of the intended research use of their donated biospecimens; however, specifics of future research may not be known at the time of biospecimen collection.

Under certain conditions described by the Office of Human Research Protections (OHRP)(see [55]), research involving the use of previously collected biospecimens and data may not be considered human subjects research, and, therefore, may not require informed consent. Essentially, if investigators are barred from accessing identifiable information pertaining to the living individuals from whom biospecimens were previously collected, then these investigators are not considered to be conducting human subjects research, and no consent for the research is required under OHRP guidance (see Section B.5.1.3. NIH Genome Data Sharing (GDS) Policy and Informed Consent Requirements). Furthermore, under DHHS regulations at 45 CFR Part 46 Subpart A [54], 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 § 46.104(d) [56] 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(e) or (f) [57].

It is critical that biospecimen resources understand, track, and are capable of adhering to the requirements of current OHRP guidance and DHHS and NIH policies regarding informed consent and data sharing, and applicable state and/or local regulations. Additional ethical, legal, and social considerations arise when participant consent is sought for biospecimen research involving the use or generation of genomic data (see the National Institutes of Health (NIH) National Human Genome Research Institute (NHGRI) website [58], [59], and Section B.5.1.3. NIH GDS Policy on Informed Consent).

B.5.1. Federal Regulations and Guidelines Pertaining to Informed Consent for Biospecimen Collection and Use

DHHS-conducted or -supported research on human subjects is regulated by 45 CFR Part 46 [60]. These regulations include specific elements pertaining to research that involves the collection of identifiable private information or identifiable biospecimens 45 CFR 46.116(b)(9). The DHHS regulations describe both when informed consent is required and what elements must be included in an informed consent process and document. Biospecimen resources should track whether appropriate informed consent is documented for each biospecimen or the reason why informed consent was not required; discrepancies in the consent status should be resolved prior to use of the biospecimen in research (see the OHRP Website for guidance on informed consent [61]).

Revisions to the DHHS requirements, effective January 21, 2019, include a "broad consent" regulatory pathway for limiting the required IRB review for the storage and future secondary research uses of collected

biospecimens, under certain specified conditions (45 CFR 46.116(d)). The OHRP has issued FAQs and guidance on these DHHS-informed consent regulatory requirements [57, 62, 63].

B.5.1.1. DHHS Informed Consent Provisions

The DHHS implemented additional and specific consent provisions pertaining to the collection, storage and future uses of biospecimens. These include:

- Why particular biospecimens and data are being sought and why human subjects are being asked to participate (45 CFR 46.116(b)(1)).
- The nature of the procedure during which the biospecimens will be collected, including if a biopsy procedure is mandatory, whether it has a clinical purpose, or whether it is solely for research purposes; for example, whether the biospecimens will come from leftover tissue from a surgical procedure or from an additional research procedure (e.g., a biopsy solely for research purposes) (45 CFR 46.116(b)). In January 2025, the U.S. Food and Drug Administration (FDA) and DHHS jointly issued a *Draft Guidance on Considerations for Including Tissue Biopsies in Clinical Trials* [64].
- That patients have the right to refuse biospecimen donation, and that this will in no way influence their care, treatment, or eligibility to participate in other clinical research studies or clinical trials (45 CFR 46.116(b)(8)).
- If known, specific descriptions of the nature and purpose of the research.
- Requirement to inform subjects whether biospecimens (even if identifiers are removed) might be used for commercial profit and whether the subject will or will not share in this commercial profit (45 CFR 46.116(c)(7)).
- Whether future research with the biospecimens will or might include whole genome sequencing and the nature of any special privacy risks associated with proposed genomic profiling research technologies if such research is anticipated (45 CFR 46.116(c)(9)).
- A clear description of the operation of the biospecimen resource, including whether identifiable information will be maintained by the biospecimen resource.
- Whether identifiers could be removed from collected biospecimens in the future and then used for research without any additional consent (45 CFR 46.116(b)(9)).
- Whether there is a policy or plan for offering the return of any individual results, including clinically relevant results (45 CFR 46.116(c)(8)) or incidental findings (See section B.6.2. Return of Individual Results).
- The conditions under which samples and data will be released to recipient investigators (see Section B.8. Access to Biospecimens and Data).
- Who may access biospecimens and associated data, including whether for-profit researchers may seek access and, if so, any policies regarding disposition of potential commercial profits (45 CFR 46.116(c)(7)).
- Procedures for protecting the privacy of human subjects and confidentiality of data (see Section B.7.3. NCI Recommendations Pertaining to Privacy and Confidentiality).

B.5.1.2. FDA Informed Consent Regulations

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 [65], 21 CFR Part 50 [66], and 21 CFR Part 56 [67]). The FDA may exercise enforcement discretion as to the requirement for informed consent for *in vitro* diagnostic device studies that utilize "leftover" biospecimens (e.g., remnants of biospecimens collected for routine clinical care or analysis or biospecimens previously collected for

another research purpose) that are not individually identifiable if certain conditions have been met.[3] Key conditions include ensuring that no identifiers are retained and that specimens were collected without additional risk to subjects solely for research.

B.5.1.3. NIH Genomic Data Sharing (GDS) Policy and Informed Consent Requirements

For samples collected on or after the effective date of the NIH GDS Policy (January 25, 2015), NIH expects that research participants have given explicit consent for their genomic and phenotypic data to be used for future research purposes and shared broadly, and that the data will be submitted to an NIH-designated repository. Consent is required even for cell lines or clinical samples/biospecimens that are de-identified. If consent was obtained but does not fully align with the NIH GDS Policy, then the samples cannot be used for research falling under the Policy, with rare exception. NIH Guidance on the GDS Policy consent requirements is available [68].

The NIH GDS Policy consent requirements are consistent with the NCI Best Practices described in Section B.5.2 below (see Section B.5.2. General NCI Recommendations Pertaining to Informed Consent), in requiring that informed consent should address:

- How the biospecimens will be used and whether they may be used in secondary research studies.
- How the data collected or generated from biospecimens will be shared.
- Who may access biospecimens and associated data, including whether for-profit research may seek access.
- Biospecimen resources utilizing a "one-time general consent" strategy to streamline consent for future unspecified research uses is consistent with the NIH GDS Policy (see Section B.5.1.3. NIH GDS Policy on Informed Consent).

Under the NIH GDS Policy [69], any restrictions on participant consent for future research uses of data must be captured in the data use limitations that accompany the data when it is submitted to an NIH-designated repository, via the institutional certification process [70]; however, these requirements only apply to projects that fall under GDS (see also B.7.3.2. Certificates of Confidentiality).

B.5.2. 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 actively in the informed consent process, whereas others store biospecimens that were originally collected under separate consenting processes conducted by researchers not affiliated with the resource. Regardless of the level of involvement in the informed consent process, biospecimen resources should ensure that any research uses of biospecimens that are in their custody or control for any period are consistent with the original informed consent agreements of the biospecimen contributors.

B.5.2.1. Accommodating Research Participant Preference

The NCI recommends seeking the informed consent of research participants who contribute biospecimens and associated data not only whenever such consent is required by regulation, but also whenever consent is ethically appropriate and can practicably be obtained. Respect for individuals who have provided data and/or biospecimens for research is of paramount importance; therefore, the preferences of contributors, as individuals and as members of groups or communities, should be considered when deciding whether informed consent should be sought or waived. Some individuals or groups may want only to contribute to single research projects, while others may prefer to contribute to multiple types of research. Within the

[3] Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens That Are Not Individually Identifiable. See https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-informed-consent-in-vitro-diagnostic-device-studies-using-leftover-human-specimens-are-not. See also https://www.fda.gov/media/122648/download.

latter group, some may want to offer their biospecimens at the outset for a wide range of future research (and avoid being recontacted later for additional consent) while others may wish to be actively engaged in future decisions about the use of their samples. The biospecimen resource should have transparent policies concerning the informed consent process. These policies should include when consent will be sought from research participants, when input from community or tribal representatives should be solicited, and when permission from the next of kin of deceased research participants should be sought.

B.5.2.2. Respecting the Beliefs of the Research Participant

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 remain whole upon death [71-73]. Investigators should consider the religious, cultural, and spiritual views and practices of communities when planning a research study that will include the collection of biospecimens and data. In particular, researchers should inquire whether there are any concerns among biospecimen contributors regarding the use, disposal, or return, if practicable, of research biospecimens. In order to ensure that the wishes of research participants are upheld, biospecimen resources should track any relevant restrictions or instructions based on these types of beliefs.

B.5.2.3. Timing

For biospecimens collected during medical care, the timing of consent (e.g., before or after a medical procedure) to obtain biospecimens for research purposes should be informed first by ethical considerations, and second by logistical constraints. Consent should generally not be sought when a patient has just received a serious diagnosis. Generally, consent should be obtained prior to the medical procedure during which biospecimens and data will be collected, but post-procedure consent may be appropriate in some cases [74]. 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 completely comprehend what was being asked. However, prior informed consent would be required in cases where biospecimens are collected from research participants specifically for research purposes or when the procedure for collecting biospecimens for clinical purposes is modified to meet a research need, unless an IRB grants a waiver of the requirements for obtaining informed consent.

B.5.3. NCI Recommendations on Key Elements for Informed Consent Documentation

The informed consent document for the collection and future research use of biospecimens should balance the requirement to provide sufficient information to research participants to make an informed decision with the need to ensure that the document is comprehensible and reasonable in length. Broad and appropriate use of research data is strongly encouraged by the NIH's data sharing policies. When designing the informed consent for a new research project, investigators should consider potential future research using banked specimens (NIH Data Management and Sharing Policy [75]). The elements described below may be modified depending on the nature, scope, and mission of the biospecimen resource.

B.5.3.1. Scope

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

The informed consent document should specify the following:

- Who will be the custodian of the biospecimens and associated data, and what will be their role(s)?
- How the obtained biospecimens and data are intended to be used, and whether they may be used in the future for currently unknown secondary research aims.
- What types of data will be collected, and how will the data be used, stored, and shared?

- Information about policies governing the retention of biospecimens, e.g., how long biospecimens will be stored, if known, or whether storage is intended to last indefinitely until distributed for research.
- Whether there is a policy or plan for producing a lay summary of the aggregate study findings, and where the research participant may find, or how they may receive, the summary.

B.5.3.2. Longitudinal Data Collection

Where applicable, the informed consent document should state whether identifiable or coded information will be linked to other data about the research participant, such as clinical data obtained from anatomic pathology and clinical pathology laboratory information systems, cancer registries or electronic health records (see Section C.5.3. Longitudinal Clinical and Epidemiological Data for further recommendations on the integration of informatics systems). If longitudinal data will be collected by accessing the participant's medical records, then participants must be clearly informed about the nature, frequency, and sources of the data collection, and the informed consent document should clearly state this.

B.5.3.3. Contact Subsequent to Collection

If appropriate, the informed consent document may include an option that allows research participants to select whether they would be willing to be recontacted to collect additional information, such as lifestyle or social determinants of health information, or about the use of their biospecimens and/or data in future research studies (see Section B.5.4.3 Dynamic Consent).

B.5.3.4. Future Research

Biospecimen resources collecting samples and data for future research use should explain to prospective biospecimen contributors how their biospecimens may be used in the future, including any potential anonymous uses, meaning that all identifying information has been removed with no possibility to link back to identifiers.

B.5.3.5. Genetic Analysis

In research analyzing the deoxyribonucleic acid (DNA) of donated biospecimens, it is possible that information could be discovered that relates to research participants' families, communities, or broader population groups. The analysis of such genetic data could potentially create additional risks to participants, such as discrimination and/or stigmatization or breaches of privacy. The informed consent document should state whether there is a risk that individual genetic results generated as part of their research participation could potentially impact participants' families and communities. 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 research participant posed by such research, if applicable (See 45 CFR 46.116(c) [69, 76]. The Genetic Information Nondiscrimination Act (GINA, [77]) 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, life insurance, or long-term care insurance. For more information on GINA, please refer to the guidance from the OHRP [78] and the discussion of genetic discrimination and GINA on the NHGRI website [79]. Note that NHGRI provides consent templates and model consent form language [80].

B.5.3.6. Considerations when Returning Results

The informed consent document should state whether aggregate research results (summarized data based on biospecimens from multiple contributors) or individual results will be returned to the research participant, the participant's healthcare provider, and/or the participant's family members and, if so, the mechanism for communicating such results, e.g., e-mail, U.S. mail, newsletter, telephone call, genetic counselor, etc. Individual results may range from primary diagnostic findings or discrepancies to

secondary "incidental" findings unrelated to diagnosis or even to study aims (see Section B.6. Return of Results). Any procedure for opting out of the receipt of incidental findings or individual results should be clearly indicated. The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule [81] and the Clinical Laboratory Improvements Amendments (CLIA, [82]) affect whether individual results can be offered or disclosed.

B.5.3.7. Online Disclosure of Policies and COIs

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 Website or provided in a brochure that accompanies the informed consent document (Also see Section B.10. Conflict of Interest (COI)).

B.5.4. Approaches for Seeking and Obtaining Informed Consent

The overall respectful, transparent, and informative process for seeking and obtaining informed consent should be considered a critical adjunct to the informed consent form itself; participants may perceive the process to be more important than the form itself [59]. There are many ways to seek and obtain consent from individuals for the research uses of their biospecimens and associated data. Seeking permission from clinic patients, during their routine visits, to be contacted for participation in future biospecimen research studies can be an appropriate patient engagement mechanism and has received high acceptance from patients; in this approach, biospecimen resources may utilize a "permission to contact" strategy whereby potential research participants are approached for their general agreement to be contacted in the future about research participation, with later follow up as appropriate for participation in specific research studies [83].

B.5.4.1 Tiered Approach

A tiered or "meta" consent approach allows research participants to choose among different levels or types of participation, such as limiting the types of research for which their contributed biospecimens can be used, or whether to allow or decline future recontact for additional studies [84].

With tiered consent tracking, the participant's choices should be made and recorded accurately and be easily retrievable at the time of retrieving specimens for use. This requires an informatics system that tracks, for each study protocol, the choices and limits made by each research participant to ensure that his or her wishes are explicitly honored. While a tiered consent process may allow the research participant greater autonomy, it also can lead to ambiguities in terms of how to classify certain types of research, especially when considering that research approaches and technologies evolve over time. Tiered consent may be burdensome on the biospecimen resource if the purpose of the biospecimen resource is to provide biospecimens for a broad range of research.

B.5.4.2 Electronic Consent

The use of electronic consent (also known as eConsent) should be considered as there may be many benefits to the institution and to the participant [85, 86]. eConsent strategies may broaden participant options and may streamline the consent process and improve participant understanding of consent information [85, 86]. The use of eConsent allows for easier tracking for regulatory compliance purposes, for consent form versions, signatures and dates. Some eConsent platforms provide multimedia presentations such as video and audio, along with written text, which allow for different learning styles, different languages and addressing cultural differences. eConsent should be piloted for usability and understanding by the targeted donor community. Implementing eConsent may also be as simple as using a remote e-signature tool in conjunction with a written consent form. eConsent can be provided in person using a device, such as a tablet. eConsent is not a substitute for the personal interaction between study staff and the participant. eConsent can be provided remotely, when it is not feasible to interact in person, or to limit the physical time spent together in person, a method that proved valuable during the COVID-19

pandemic [87, 88]. Developing a secure, privacy-compliant eConsent that meets security regulations may require significant resources.

B.5.4.3 Dynamic Consent

Another consent approach that allows greater specificity and more choices for the use of biospecimens in secondary research is "dynamic consent," whereby participants are initially consented for one or more specific studies and then recontacted, typically electronically/online portal or via mobile technologies/apps, for permission to participate or use their biospecimens in new studies [89]. Dynamic consent processes may increase participant engagement over time by providing additional information and increasing research transparency. This type of consent may allow participants to make more informed choices regarding the use of their biospecimens, as their choice is made prior to their samples being used. For a biospecimen resource of substantial size, developing a digital platform to support easy to access and secure communication with participants regarding their choices for biospecimen use may be useful. However, implementing dynamic consent at scale requires secure, user-friendly digital platforms capable of managing ongoing participant communication. Newly proposed models of consent incorporate dynamic consent concepts with generative artificial intelligence to construct applications for custom informed consent and longitudinal engagement [90]. Reported shortfalls of such models include that they may amplify an existing "digital divide" between research participants who do and do not regularly access online resources, that customized consent may prove difficult or impossible over time to understand and track over time by ethics boards and biobanks, and that such approaches may confuse participants and consequently engender distrust over time [91-93].

B.5.5. Issues Pertaining to Research Biopsies

If biopsies are planned as part of the biospecimen collection protocol, the informed consent should include information regarding biopsy procedures: whether collections will be made only during biopsy procedures that are clinically indicated or whether biopsy procedures solely for research purposes will be conducted. The consent process for the collection of biospecimens for research during biopsy procedures should be a separate interaction from the consent process for the clinically ordered biopsy. Ideally, the process should be conducted by a person other than their clinical healthcare provider to avoid any appearance of undue influence. For minors, there has been controversy and no clear guidance on whether it is ethical to take biopsies solely for research purposes [94]. The risks and benefits to the minor participant should be weighed when making this decision. For adult participants, obtaining research biopsies through high-risk procedures may be advisable only if the biopsy is clinically indicated. Regardless of what the participants agreed to during the informed consent process, they should always be allowed to decline collection of biopsies for research purposes at any time and should be allowed to continue in the study, if feasible and consistent with the study protocol. DHHS and FDA have issued draft guidance on Considerations for Including Tissue Biopsies in Clinical Trials [64].

B.5.6. Informed Consent 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 potential need for obtaining informed consent when the research participant reaches the legal age to consent [95, 96]. Under 45 CFR 46 [76], 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.[4] However, the IRB may consider whether a waiver of informed consent under 45 CFR 46.116(d) [57] is appropriate. In addition, the following operational best practices related to this issue should be considered when developing a biospecimen resource:

[4] See the OHRP frequently asked questions related to this topic at: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/45-cfr-46/index.html.

- Biospecimen resources that plan to store identifiable biospecimens from children should consult with their IRB 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 research participants to obtain consent at the age of majority, which necessitates that, whenever possible, accurate contact information is maintained. Where practicable, 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 the contribution of pediatric biospecimens for research should clearly state whether recontact and consent will be attempted once the child reaches the age of majority. For longitudinal studies or pediatric research otherwise involving periodic visits over the long term, protocol planning should consider the need to seek consent when children reach the age of majority.
- Consent forms may include options for research participants to consent to the future research use of their biospecimens. For example, NCI's Childhood Cancer Data Initiative's Molecular Characterization Initiative [97] uses the Children's Oncology Group's Project: Every Child protocol (APEC14B1) and consent [98], which provides options for research participants to allow research on banked specimens after the initial CLIA sequencing and return of results.

B.5.7. 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 OHRP [99] and FDA guidance [100]. Participation in research includes the collection of biospecimens and/or of individually identifiable private information from 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 research participant's ability to discontinue participation in research and describe what will take place should this occur. In turn, biospecimen resources should develop standard operating procedures (SOPs) on how a request to discontinue participation in research will be handled, including processes to verify that the SOP was followed and mechanisms for documenting that a participant discontinued participation and that all appropriate measures for the biospecimens and data were taken.

- Discontinuation of participation in research may be complete or partial. In some cases, the 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. The research participant should be offered a choice as to whether to limit their discontinuation to future interventional and/or interactional activities, or to proceed with a full and complete discontinuation of participation. Interactional activities would include any contact with the participant, including collection of biospecimens. Non-interventional research activities may include collecting medical information from their medical record and use of their previously collected biospecimens and data.
- A research participant may choose to discontinue all research participation, thus prohibiting any future contact, collection of biospecimens, collection of medical information, and use of previously collected biospecimens and data. If this is the case, 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. Notably, analysis of data generated from biospecimens distributed to researchers prior to the date of discontinuation of participation is generally not prohibited, provided that such analysis falls within the scope of the analysis described in the IRB-approved protocol.

- If a 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 whenever possible. In the case of American Indian and Alaska Native participants, special tribal requirements should be included [101]. The informed consent document should clarify whether it is the policy of the biospecimen resource to destroy biospecimens in the event of a research participant's discontinuation of participation in research or if the participant will be offered the choice to either destroy previously collected samples or allow the use of the samples in 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 B.5.2. General NCI Recommendations Pertaining to Informed Consent).
- Data sharing policies and practices, intended to accelerate research progress, can complicate or prevent the removal of data from a biospecimen resource or associated data resource when a research participant withdraws from a study. For example, if data has been shared in a genomic database and distributed to researchers, the data may already have been analyzed or may already be part of a dataset that is included in a published scientific manuscript. Withdrawing an individual research participant's data, thus, may be difficult or impossible. That said, biospecimen resources and associated data resources should make every effort, when requested, to remove the individual's data from future data releases. In considering any request to purge stored data, biospecimen resources and associated data resources should consider whether such action would be possible given the information at hand linking the biospecimens to the individual and the state of data-sharing activities.

B.6. Return of Results

B.6.1. Return of Aggregate Results

Contemporary ethical and societal perspectives emphasize that researchers and research organizations, including biospecimen resources, should consider making greater efforts to provide ongoing communication about the progress of research studies to research participants and their communities. The return of aggregate research results, defined here as the sharing of information and results of a study at large, without identifying individual data, can represent a significant return of value to research participants and the medical institutions that support research studies. The return of aggregate results is exemplified in the NCI Cancer Moonshot Biobank study, which provides study progress metrics on the study website [102], through a participant newsletter, and to contributing medical institutions in the form of an annual report. Such engagement strategies aim to increase participant and provider knowledge of research progress and the value of their participation and may potentially enhance the perceived trustworthiness of the research study, investigators, and biospecimen resource [17]. Biospecimen donation with informed consent is often thought of as a one-time interaction; however, for some longitudinal studies and for work with some communities, the informed consent and biospecimen donation can be considered the beginning of a longer-term relationship with the donor and/or their community [48, 103]. The maintenance of an ongoing relationship with research participants and their communities is a critical engagement concept that can be supported with the return of aggregate results.

Planning for the return of aggregate results should involve the researchers who will be conducting the research that will generate results and may or may not require the participation of the biospecimen resource. Regardless of whether a biospecimen resource is preparing to share results with research participants, it is important that the resource is forthright about their policy.

B.6.2. Return of Individual Results

Participants often want to benefit from their participation in research and may wish to receive information that may be beneficial to their health and/or the health of their family members. When asked if they would like results returned to them from research studies, participants almost always respond yes [104-107]. The return of individual results can be viewed as a recognition of the participant's contribution and a tangible return of value and has been identified as a motivating factor, along with altruism, for biospecimen donation [108, 109]. Examples of individual results may include, but are not limited to, genetic alterations identified by tumor sequencing, such as those provided to participants and providers in the Cancer Moonshot Biobank [43], potential gene-environment interactions [110-112], and histopathology findings [113-115]. Planning for the return of individual results should involve the biospecimen resource as well as the researchers who will be conducting the research.

Researchers, institutions, and biospecimen resources should carefully weigh a number of factors when considering the return of individual results, including:

- Regulatory requirements.
- Criteria for which results should be returned (e.g., clinical actionability or medical significance).
- Communication methods.
- Availability of any potential support services (e.g., genetic counseling).
- Associated costs.
- Potential psychosocial or medical impacts on the participant and their family [116].

When possible, biospecimen resources should consider returning individual results to participants to honor their participation and provide a potential benefit to their participation in research. Based on the principle of reciprocity, returning results to biospecimen contributors extends beyond a simple exchange; it has social implications in that it honors a commitment made between the participant and research investigators and acknowledges the responsibilities of the researchers and biospecimen resource [117]. In any event, a participant should always have a choice about receiving results when offered by a study and outlined in the informed consent; the process should allow participants to change their preference at any time. Approaches to the return of individual results may also need to accommodate changes over time due to new scientific knowledge, as well as differences in participant preferences across age ranges [107, 118]. Several large-scale initiatives have adopted a return of results approach, which may be informative for biospecimen resources; these include the Electronic Medical Records and Genomics (eMERGE) Network [107, 118] and NIH's All of Us program [119, 120].

At a high level, planning and decision making about the return of individual results should consider the ethical, legal, and policy implications involved in returning the results, along with any operational constraints that may be involved [121]. For example, when developing policies pertaining to the return of individual results, study investigators and their institutions should consider:

- Whether findings would be medically significant and/or clinically actionable to research participants and/or their family members.
- Whether the results generated would be analytically validated.
- Whether genetic counseling or follow-up clinical services would be needed and available.
- Whether results were obtained in CLIA-certified laboratories or could be verified through such facilities.

In the U.S., laboratories conducting clinical testing must hold accreditation under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). CLIA regulations apply to all U.S. laboratory testing sites that test human specimens for the assessment of health of human beings or to diagnose, prevent, or treat disease

[82, 122]. Any results from laboratory test results that are communicated directly to patients will be assumed to represent an assessment of the health of the patient, and therefore, CLIA regulations apply.

CLIA regulations of a laboratory site vary by the types of assays being performed. In general, the more complicated the assay, the tighter the requirements under CLIA, and sites are subject to inspection. Laboratory facilities interested in obtaining a CLIA Certificate should consult the Centers for Medicare Services (CMS) website [123]. In general, CLIA Certificates of Compliance (COC) are issued to laboratories after inspection by either CMS surveyors or state agency surveyors, and CLIA Certificates of Accreditation (COA) are issued to laboratories based on their accreditation by one of the seven organizations approved by CMS to conduct such surveys.

Biospecimen procurement and transport to the laboratory for testing is a process that, if not directly under the auspices of the CLIA testing laboratory, is overseen by the testing laboratory medical director to ensure sample integrity and maintenance of identification throughout the testing process. With regard to biospecimen procurement, processing, storage, and transport that occur within a biospecimen resource (prior to sample testing in a CLIA laboratory), it is reasonable to consider that the biospecimen resource is a part of the system that will ultimately generate a clinical result. Therefore, the biospecimen resource should either hold its own CLIA certificate (possible if the research infrastructure is conducting at least one relevant clinical assay) or, alternatively, attain accreditation by the College of American Pathologists' Biorepository Accreditation Program (BAP)[11]. The BAP is a program geared toward biospecimen resources that also may be used to obtain a CLIA Certificate of Accreditation in limited cases of CLIA-applicable human sample testing. Currently, the testing technologies covered include *in situ* hybridization, electrophoresis, polymerase chain reaction (PCR) target amplification, and histologic/microscopic evaluation and analysis.

The following issues should be carefully considered:

- Which results to return; for example, all results, or only results that are medically significant and/or clinically actionable [106, 124-126].
- Whether the determination of which results to return will be periodically reviewed over time and the approach potentially changed.
- Where and how the results will be generated.
- If initial results need to be confirmed in a CLIA-certified laboratory before results are returned to the participant, how confirmatory testing will be funded.
- The potential impact on the participant and their family upon receipt of the results, including potential emotional, financial, or insurance-related consequences.
- Who will provide the results to the participant, to their provider, or both, and what methodology will be utilized to communicate the results (e.g., phone calls, a secure health portal, in person).
- Whether counseling or other medical support will be provided to the participant or their family; ideally, the person(s) providing the results will be trained in communicating such results to participants and/or their families.
- If and how results will be communicated to family members in the case of a participant's death.

B.6.3. Incidental Findings

During the course of a research study, it is possible that unexpected discoveries may be made that could have bearing on the health of a research participant and/or their family members. When such findings are discovered and are outside the initial scope and/or timing of the research study's objectives, an ethical need to return the results to the participant may arise [106, 114]. Governance plans should address the possibility of such incidental findings and the plans for addressing such findings.

Plans should consider:

- Whether samples are de-identified and thus not traceable to individuals.
- Whether findings can be validated analytically and clinically.
- The feasibility of communicating findings after study completion or sample collection.
- Whether the informed consent process anticipated the potential for incidental findings and allowed for recontact.

In some cases, pragmatic or ethical limitations (e.g., de-identification, lack of clinical validation, or participant preferences) may preclude returning incidental findings, and this should be transparently disclosed in the study protocol and consent materials. For genomic incidental findings. consensus guidelines have been developed by the American College of Medical Genetics and Genomics (ACMG) [127, 128]. Recommendations and guidance on the return of incidental findings are also available from the DHHS [129].

B.7. Privacy and Confidentiality Protections

B.7.1. Confidentiality and Security

The ethical framework for biospecimen research depends in part on protecting the privacy of individuals who contribute biospecimens and on maintaining the confidentiality of associated clinical data and information [130]. Applying the highest possible ethical and operational privacy standards is necessary to ensure the trust, support and participation of research participants, clinicians, researchers, and other stakeholders in biospecimen resource activities. Biospecimen resources should implement clear policies for maintaining the confidentiality and security of the biospecimens and associated clinical data. For example, biospecimen resources that store coded samples and data should establish policies regarding how the link or code that allows identification of research participants will be secured. Transparency about the measures undertaken by a biospecimen resource to assure confidentiality may be beneficial to stakeholders. Participants, for example, may be unaware that multi-level coding (e.g., double- or triple-coding) may be performed in an effort to greatly decrease the possibility of re-identification risks [131]. Considering the continued advances in genomic and proteomic technology, the increase in sharing of biospecimen-associated data, and the reliance of biospecimen resources on electronic and Web-based databases for data tracking, it is important to address the risk of breaches in privacy. The unintended release or disclosure of sensitive information, in some cases, could place individuals at risk for discrimination and related groups at risk for stigmatization, particularly in genomic or behavioral studies, although the frequency of these types of harms is unknown [131, 132].

B.7.2. Federal Regulations Pertaining to Privacy

The DHHS-issued regulation titled “Standards for Privacy of Individually Identifiable Health Information,” commonly known as the HIPAA Privacy Rule (see 45 CFR Part 164 [133] and Subparts A and E of Part 160 [134]), was created to protect the privacy of health information that identifies an individual while permitting essential societal functions, including biomedical research. Although the HIPAA Privacy Rule does not apply to biospecimens directly, it may affect biospecimen resources that are considered “covered entities” (e.g., hospitals, clinical laboratories) or “business associates” of covered entities, in that human specimens often are accompanied by identifiable protected health information (PHI). For more information on the application of the HIPAA Privacy Rule to research repositories and databases, see [135]. 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 HIPAA Security Rule, is required to ensure appropriate safeguarding of electronic PHI (see 45 CFR Part 160 and Part 164 Subparts A and C [133, 134]. Detailed information on the HIPAA Security Rule is available at [136].

In January of 2013, the U.S. DHHS issued the Omnibus Final Rule implementing key amendments to HIPAA enacted under legislation known as the Health Information Technology for Economic and Clinical Health Act (HITECH). The HITECH amendments to HIPAA introduced several provisions relevant to biospecimen research and the creation of biospecimen resources for future research, including enhanced privacy protections

and broader enforcement capabilities. They also clarified the responsibilities of business associates and strengthened requirements for breach notifications. The rule was published in the Federal Register and is available at [137].

The European General Data Protection Regulation (GDPR), enacted in May of 2018, broadly protects the personal data security and privacy interests of individuals, including in the context of biomedical research. While the GDPR contains a research exemption and acknowledges the need to facilitate scientific research, biospecimen resources that distribute and/or access non-anonymized samples or data to or from the European Union member states should consider their compliance obligations under this omnibus privacy protection law [138].

B.7.3. NCI Recommendations Pertaining to Privacy and Confidentiality

B.7.3.1. Policies

Biospecimen resources should establish clear policies for protecting the confidentiality of identifiable information. These policies may include data encryption, coding, establishing limited access tiered or role-based data access by biospecimen resource employees, and use of nondisclosure agreements. An honest broker model, defined as an individual or system that provides de-identified samples and/or data from a biospecimen resource to the researcher, if appropriate, should be considered for sharing samples and data to protect research participants' privacy [139, 140].

B.7.3.2. Certificates of Confidentiality

Biospecimen resources may apply for "Certificates of Confidentiality (CoCs)" to protect identifiable research information from forced disclosure. Under section 301(d) of the Public Health Service Act [141] (42 USC 241(d)), the NIH may issue CoCs to authorize persons engaged in biomedical, behavioral, clinical, or other research to refuse to disclose identifying information about research participants in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding. Effective October 1, 2017, CoCs are issued automatically for any NIH-funded project using identifiable, sensitive information that was ongoing on or after December 13, 2016 [142].

CoCs 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. They may not be necessary for all biospecimen resources, particularly those only housing fully de-identified samples. If a CoC is obtained, this should be explicitly stated in the informed consent document. Further information about Certificates of Confidentiality may be found at [143].

B.7.3.3. Documentation

Biospecimen resources should document their policies for maintaining the privacy of research participants and the confidentiality of associated clinical data, including descriptions of mechanisms for auditing effectiveness, enforcement measures, and explicit agreements not to release code keys or not to attempt reidentification of individuals from de-identified data (see the database of Genotypes and Phenotypes (dbGaP) Code of Conduct [144] as an example).

The level of security should be appropriate to the type of biospecimen resource and the sensitivity of the data it houses. Genetic data, in particular, may involve additional risks such as discrimination and/or stigmatization, and these concerns may have an impact on research participants' families or broader population groups. De-identification of research data cannot completely eliminate the risk of re-identification given the growth of publicly available and electronically shared databases, as well as evolving technologies for linking different types and sources of data [145-147]. Respect for research participants requires transparency about the tradeoffs between limiting access to individual medical data and facilitating the greatest utility of such data in research [132, 148].

B.7.3.4. Compliance

Biospecimen resources should comply with all applicable federal, state, and local statutes and regulations pertaining to privacy. Biospecimen resources that collect, store and/or facilitate access to large-scale human or non-human genomic data derived from NIH-funded research must also comply with the relevant mandates of the NIH Genome Data Sharing Policy [69] and broader NIH policies for data management and sharing [149].

B.7.3.5. Data Access System

Biospecimen resources should use a data access system with defined levels of access privileges for biospecimen resource staff in order to protect the confidentiality of research participants and their associated data, tailored to the sensitivity of the data.

- Access levels for biospecimen resource staff should be described in the protocol for operation or Standard Operating Procedures (SOPs) of the biospecimen resource and approved by an IRB and/or a bioethics/scientific advisory board, as appropriate.
- Access to sensitive participant data, such as identities and medical, genetic, social, and personal histories, should be restricted to only those biospecimen resource staff members who must 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 all access should be appropriately monitored to ensure compliance.

B.7.3.6. De-identification

Data submitted to an NIH-designated repository under the GDS Policy [69] must be de-identified according to standards set forth under the regulations for the protection of human subjects at 45 CFR 46, as well as the requirements of the HIPAA Privacy Rule. In addition, NIH has obtained a CoC for dbGaP as an additional precaution because genomic data can be re-identified [150-152]. Similar precautions to protect the privacy of the research participant should be undertaken for other types of data that may be associated with biospecimens, including sanitizing image data and clinical record redaction.

Elements of the GDS Policy and the Supplemental Information to the NIH Policy for Data Management and Sharing [153] should be clearly communicated in the informed consent, consistent with NCI recommendations that the informed consent document disclose whether biospecimens may at some point be re-identified (see Section B.6.3.6. De-identification) and explicitly state if a CoC has been obtained (see Section B.7.3.2. Certificates of Confidentiality). Additional resources on de-identification include guidance from DHHS [154] and NIST [155], guidance on images from NCI's Cancer Imaging Archive [156], and a clinical text de-identification tool from the National Library of Medicine's (NLM-Scrubber)[157].

B.8. Access to Biospecimens and Data

Biospecimen resources have an ethical obligation to make their best efforts to use, or distribute for use, their collected biospecimens and associated data in accordance with the terms under which research participants consented [158, 159]. Research participants donate their biospecimens with the understanding that the materials will be used in meritorious research, and timely access to human specimens and data is crucial for research fields such as genomics, proteomics, metabolomics, molecular imaging, and others. 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 and data access and distribution that are consistent with ethical principles, governing statutes and regulations, informed consent language, and research need.

Guidelines for sample and data access should have the following characteristics:

- *Clear* to ensure their comprehension and adoption.

- *Flexible* to allow application to different and evolving scientific needs.
- *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 why, and what justifications should be provided in the requests for biospecimens. These guidelines should be developed for all new collections and, whenever practicable, for existing collections. Access procedures should be fair, transparent, and clearly communicated. Such guidelines and procedures should be included in governance plans and on website(s) for the biospecimen resource or the specific collection.

Biospecimen and data access policies and procedures may differ between the multiple studies that a biospecimen resource manages and should align with the original informed consent for each study. To respect the valuable donations made by participants, these policies and procedures should be developed prior to specimen collection and reviewed periodically over the life of any study. Indeed, as much thought and planning should go into the plans for distribution as the plans for collecting the biospecimens and associated data.

B.8.1. Access to Biospecimens

B.8.1.1 General Principles for Biospecimen Access Decisions

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

- Consideration of the overarching principle that research participants have donated biospecimens with the expectation that the samples will be used in research.
- Timely, fair, ethical, and appropriate access to human specimens, without undue administrative burden.
- Evaluation of institutional research qualifications and resources, to carry out the proposed research plan.
- Sufficient investigator funding to carry out the proposed research plan.
- Proven investigator experience with the proposed methodology.
- A research plan with scientific merit that is appropriate to answer the study question, and for which the requested biospecimens and associated data are suitable, and which falls within the appropriate time limit for use.
- Alignment of requested use with the informed consent and overall objectives of the study.
- A mechanism for addressing disputes over access decisions.
- An investigator agreement covering confidentiality, conduct, use, disposition, and security of biospecimens and associated data.
- The parties' written agreement in a Material Transfer Agreement (MTA), a legally binding agreement that is used when biospecimens are shared or transferred, or other appropriate document that is consistent, as applicable, with the NIH Research Tools Policy [160] and other applicable NIH sharing policies [161]. See also Section B.9.1. Material Transfer Agreements.

B.8.1.2. 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 may be considered by the biospecimen resource in access decisions:

- Compliance with protocol-specific requirements needed to achieve study goals before other access is considered.

- If applicable, use of standardized, validated research biomarker assay methodology.
- Statistical evaluation showing that the study question can be addressed with the samples and associated data available and providing clarity that the statistical assistance needed will be available to the investigator(s).
- Confirmation that an investigator has obtained funding and IRB approval for the project, if applicable and practicable (for information on application for and exemption from IRB approval, see OHRP guidance [162]).
- Agreement that the investigator will publish or provide public information about the project outcome according to the original study objectives as well as applicable NIH policies, which may include the Research Tools Policy [160], the Revised Policy on Enhancing Public Access to Archived Publications Resulting from NIH-Funded Research [163] (see [164] and the 2013 update to the policy [165]), and NIH Data Management and Sharing Policies [75]. Of note, the NIH Research Tools Policy and the Genomic Data Sharing Policy permit reasonable short-term publication delays, e.g., to file a patent or allow a collaborator to review a manuscript. Overall, research plans should address data sharing, which will be of interest to the IRB, and the investigator should inform the biospecimen resource if they are required to broadly share generated data.

B.8.1.3. Access Policies

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

- The MTA (see Section B.9.1. Material Transfer Agreements) should include explicit data security and confidentiality provisions (see [166] for OHRP guidance on coded biospecimens).
- Policies should be consistent with the NIH Research Tools Policy [114] and other applicable NIH sharing policies [161].
- Systems should exist to ensure that research use of biospecimens is consistent with the research participant's consent for the use of his/her biospecimens, including procedures to identify if and when that research participant has revoked consent for future research use.
- Biospecimen resources should, ideally, have plans in place prior to collection for how the collected samples can and should be used for research.

B.8.1.4. Depletion of Biospecimens

The use of biospecimens while pursuing research goals will predictably reduce inventory; in fact, depletion of biospecimens for research purposes can be an important goal of a biospecimen resource. Planned depletion of biospecimens may be necessary or even desirable for research activity, quality control, or inventory control. Planned depletion should be well-documented and proceed according to policy. Policies should be established for when biospecimens have fulfilled their original purpose and/or are no longer suitable for their intended purpose, and when participants request the withdrawal of their biospecimens (see Section B.12. Legacy and Contingency Plans). Depletion should be tracked and periodically reviewed to avoid unplanned, unintentional depletion. Research with rare or limited biospecimens, for example, could result in rapid depletion of a resource.

Biospecimen resources should establish policies and procedures that reduce the likelihood of unintentional depletion, including:

- Prioritization of biospecimen requests (e.g., by scientific merit, study type, funding).
- Consideration of the risk of depletion when evaluating biospecimen requests.

- Implementation of a mechanism (manual or automated) to provide alerts when vial counts or volumes approach minimums.
- For clinical studies, consideration of any potential future need for biospecimens to facilitate a participant's additional clinical care, for example, evaluation for clinical trial entry.

B.8.1.5. Availability of Biospecimens

Biospecimen resources should make efforts to publicize the materials they have available for research, consistent with the informed consent and objectives of each study. The existence of biospecimens may be made public through the resource's Website and/or national directories such as the NCI Specimen Resource Locator (SRL)[167], which serves as a centralized listing of biospecimen resources. NCI Funded Cohorts are required to facilitate access to specimens through the Cancer Epidemiology Descriptive Cohort Database (CEDCD)[168] or a separate Web Page. Another example of an online biospecimen resource is the NCI's National Clinical Trials Network (NCTN) Navigator, a web-based resource that provides access to high-quality, clinically annotated biospecimens from NCTN trials [169]. It is designed for investigators conducting hypothesis-driven correlative research. Complementing Navigator is the NCTN Biospecimen Catalog [170], a comprehensive and searchable resource that lists available biospecimens across all NCTN Biobanks for secondary research use. Search results from the catalog direct investigators to the appropriate channels for accessing specific biospecimens, either through NCTN Navigator or directly via the relevant NCTN Group Biobank. This catalog includes biospecimens from NCTN trials already integrated into the NCTN Navigator system as well as additional biospecimens from NCTN trials not yet included in Navigator. Ideally, any restrictions on accessibility to stored biospecimens should be indicated in such tools.

The biospecimen resource should be acknowledged by the investigator in all publications that include research data from the supplied biospecimens; investigators should also express gratitude to participants for their contributions.

B.8.2. Access to Associated Clinical and Research Data

B.8.2.1 General Principles for Data Sharing

The broad or limited sharing of de-identified clinical data and research data derived from biospecimens can be extraordinarily valuable to the scientific community. The NIH Genotype-Tissue Expression project (GTEx)[171] is an example where broad sharing of genomic data from up to 50 different tissues of 1000 deceased "normal" donors has enabled the publication of thousands of research studies relevant to many different diseases (for examples, see [115, 172, 173]). Access to such a large, valuable dataset has also enabled the development of new tools and approaches in computational biology [174, 175]. Examples of NIH and NCI resources for data sharing include the dbGaP [176], the Cancer Research Data Commons (CRDC)[177] and its multiple specific data nodes, The Cancer Imaging Archive (TCIA)[178], and more. Some research programs may generate and share several different types of associated data. For example, the NCI Cancer Moonshot Biobank [43] shares de-identified demographic, clinical, and analytical data via dbGaP [176] and the Clinical and Translational Data Commons [179], part of the NCI CRDC; radiological and histological imaging data are shared via TCIA [178] and the Imaging Data Commons [180]/CRDC.

B.8.2.2 Data Sharing Policies and Approaches

Policies and approaches for data sharing must be accurately described in the informed consent for any study, with the provision that available data repositories and resources may change over time, even over the course of a single study. Different data access restrictions and policies may be required for different types of data, depending on the informed consent for the study, the nature of the data, and the potential for re-identifying research participants. Investigators requesting biospecimens and associated data may need to comply with policies that require further distribution of new data resulting from their study, which in turn may depend on what future research and data sharing are permitted by the consent. Biospecimen resources

should also consider alignment with FAIR (Findable, Accessible, Interoperable, Reusable) principles for biospecimen-associated data [181]. The challenges for biospecimen resources in aligning with FAIR principles have been recently described [182-184].

Under the NIH GDS Policy [69], human data in an NIH-designated repository is available to the broader scientific community under controlled-data access (unless otherwise specified, consistent with participant consent). Requests for controlled-access data are reviewed by an NIH Data Access Committee (DAC) and are granted based primarily on whether the proposed research use is consistent with the data use limitations that align with the informed consent. NIH DACs do not assess scientific merit, only whether the proposed research falls within the permitted use scope. Investigators who are granted access to data in an NIH-designated repository must comply with the terms and conditions for the use of the data as set forth in the Model Data Use Certification Agreement [185, 186]. Accessing investigators must also abide by National Center for Biotechnology Information security best practices [187]; notably, investigators applying for controlled data access must pledge that they will not attempt to re-identify research participants. Information about data being shared in a repository under the NIH GDS Policy should be included in the informed consent, consistent with NCI recommendations that the informed consent document describe whether data associated with or derived from biospecimens will be shared with other investigators and, if so, the oversight mechanisms for such sharing (see Section B.5.3. NCI Recommendations on Key Elements for Informed Consent Documentation) [187, 188]. The increasing use of multi-omic, multi-modal approaches to generate and share data from research participants and their banked biospecimens merits that additional considerations be taken into account beyond and in combination with genomics, such as those expectations subject to the NIH Final Policy on Data Management and Sharing effective on and after January 25, 2023.

The NCI Office of Data Sharing provides additional guidance at https://datasharing.cancer.gov/post/Guidance/nci-datasharing-guidance/.

B.8.2.3 Data Embargoes and Associated Policies

To enable future biomedical research, data and resources developed from the use of biospecimens and associated research materials (e.g., data derived from biospecimen derivatives such as nucleic acids) should remain under embargo by investigators and/or biospecimen resources only as long as necessary for legitimate and imminent research purposes. 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 Management and Sharing Policy [75], the NIH Genomic Data Sharing Policy [69], other applicable NIH sharing policies [189], and the NIH Research Tools Policy [160]. Consistent with the applicable NIH policies, completed data sets and resources should be released in a timely fashion and consistent with applicable policies (e.g., no later than acceptance for publication of the main findings from the final data set or the end of the project period, whichever occurs first). Information that is identifiable or linked to a specific individual should be shared only when consistent with the study protocol and conditions of the informed consent, using an MTA/Data Use Agreement (DUA) or other appropriate document (see B.9.1. Material Transfer Agreements), with appropriate privacy safeguards and adherence to applicable legal requirements. Under rare exceptions, a reasonable delay to ensure an investigator's publication priority or to secure intellectual property (IP) protection may be acceptable (see Section B.10. Conflict of Interest (COI)). The NCI's Cancer Moonshot Initiative [190] set more stringent data sharing and publication policies [191], in line with formal recommendations received for the initiative.

B.9. Intellectual Property (IP) and Resource Sharing

Inventions and data arising from research using biospecimens can possess significant commercial value, depending on the nature of the findings and their applicability. As researchers and industry sponsors have 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 IP policies at institutions hosting research and biospecimen resources may ultimately cause complications for biospecimen and data access, timely and open publication, sharing of research findings, and establishment of new biospecimen resources [192].

Note that receipt of Government funding, regardless of other financial sources, mandates compliance with NIH sharing policies, ensuring that biospecimens and resulting research resources and data will be available in accordance with the original informed consent and applicable NIH policies [193], including resource sharing and data management and sharing policies.

B.9.1. Material Transfer Agreements

A Material Transfer Agreement (MTA) or contract should be used for the transfer of biospecimens and data among academic, nonprofit, and/or industrial organizations, with terms consistent, as applicable, with the original informed consent, the NIH Research Tools Policy, the NIH Data Management and Sharing Policy [75], and other applicable NIH sharing policies (see Appendix 4. Sample Material Transfer Agreement). An MTA is a legally binding agreement that is used when biospecimens and associated data are shared or transferred. An MTA defines the rights and obligations of the providers and recipients of the biospecimens, documents the authority required for use of those biospecimens, and describes how the biospecimens may be used. MTAs may also address the appropriate return or destruction of unused biospecimens after the completion of the research to ensure proper stewardship and compliance with ethical standards. NIH provides examples of agreements, including an MTA for human materials and data [194]; others that capture the basic principles of the NIH policies are the NIH Simple Letter of Agreement and the Uniform Biological Material Transfer Agreement [195]. Additional examples are provided by NCI [196]. Such agreements may require appropriate modification for the transfer of human specimens. Some study protocols and/or funding bodies may require specific biospecimen and data sharing requirements for users of the biospecimens and/or data. For example, the MTA for use of Cancer Moonshot Biobank biospecimens and associated data requires that any research findings be published with public access, per the provisions of the Public Access and Data Sharing Policy of the Cancer Moonshot Initiative [191].

Basic terms in an MTA for the transfer of research biospecimens and associated data include the following:

- Identification of the contributing and receiving institutions, including, as applicable, the Principal Investigator, laboratory director, pathologist, or other responsible party, and their institution or facility with physical addresses.
- Clear descriptions of the biospecimens and/or unmodified functional derivatives thereof (e.g., DNA and ribonucleic acid, RNA) and any associated data.
- Specific assurance that the biospecimens and associated data were obtained with appropriate informed consent and IRB approval.
- A statement that the biospecimens will not be used for therapeutic purposes or transplanted into humans.
- Clear identification of the provisions relevant to biospecimen and data sharing under which the research participants were consented and associated obligations, as well as any additional biospecimen and data sharing provisions associated with the study protocol and/or policies of the funding body, and limitations, if any, on commercial use, such as production or sale.
- Agreement to abide by appropriate laws, rules, and regulations associated with human participant research and private information. These may include federal and local regulations such as the Health Insurance Portability and Accountability Act (HIPAA) [197] and 38 CFR 16 [198]and 45 CFR Part 46 [199], where applicable.
- Agreement that the recipient will not contact nor try to identify participants.

- Acknowledgement of the recipient's right, limits to, or lack thereof, to further distribute the biospecimens and associated data.
- Assurances of the end user's academic freedom and that 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.
- If applicable, a statement about acknowledging the biospecimen resource's contribution, in all oral presentations or written publications.
- If applicable, an agreement to provide annual reporting on all use of the biospecimens and data.
- A statement that biospecimens may carry infectious agents such as bacteria, viruses, etc., and should be handled by trained personnel following biohazard universal precautions.

The following web pages are relevant to this topic:

- https://grants.nih.gov/policy-and-compliance/policy-topics/sharing-policies
- https://grants.nih.gov/policy-and-compliance/policy-topics/sharing-policies/other/research-tools
- http://www.autm.net/resources-surveys/material-transfer-agreements/uniform-biological-materialtransfer-agreement/
- https://techtransfer.cancer.gov/partnering/transactional-agreements#material-transfer-agreements

B.9.2. 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, unless they have made a significant intellectual contribution to the invention. 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.

B.9.3. 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, unless explicitly stated in a prior agreement.

B.9.4. Licensing

When IP resulting from biospecimen research is exclusively licensed, a research use license should be retained to allow nonprofit and government research use and ensure access to resources and data for research and educational purposes.

B.10. Conflict of Interest (COI)

Biospecimen resources, as responsible custodians, should manage existing or potential conflicts of interest (COIs) and adhere to regulations regarding COIs at 42 CFR Part 50 Subpart F [200], as well as other applicable regulations and policies (also see Section B.10.1.1. Investigator Financial COIs). Biospecimen resources should conduct regular COI training for all personnel involved in biospecimen research to help ensure ongoing compliance and awareness.

A financial COI exists, according to Public Health Service (PHS) regulations, when a designated institutional official(s) reasonably determines that an extramural investigator's significant financial interest could directly

and significantly affect the design, conduct, or reporting of PHS-funded research (42 CFR Part 50, Subpart F and 45 CFR 94)[201, 202]. An investigator is defined by these regulations as the principal investigator and any other person who is responsible for the design, conduct, or reporting of research funded by PHS or proposed for such funding. Generally, it is the awardee institution that is responsible for maintaining compliance with the requirements of the regulations, identifying and managing Investigator Financial Conflicts of Interest and reporting them to the PHS-awarding component. Investigators disclose their Significant Financial Interests, as defined in 42 CFR § 50.603 and 45 CFR § 94.3, to their institutions. Significant Financial Interests include those of an investigator's spouse and dependent children. Extramural investigators conducting biospecimen research activities supported by PHS grants, cooperative agreements, or research contracts are subject to the requirements of these regulations (see the NIH Office of Extramural Research [203] Website 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 [204] Website for more information related to federal employees).

Notably, financial COIs may be of concern for biospecimen resources even when a study is not federally funded.

B.10.1. Financial COIs

B.10.1.1. 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 COIs, including 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 are required to adhere to institutional and PHS regulations governing COIs, including timely disclosure and management of any significant financial interests.

B.10.1.2. 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 Website or in a clear and concise manner in a brochure that accompanies the informed consent document (also see Section B.5.3. NCI Recommendations on Key Elements for Informed Consent Documentation).

B.10.2. Nonfinancial COIs

Nonfinancial COIs should be identified and managed to the extent practicable, ensuring that personal interests do not compromise the integrity of the research. An example of a nonfinancial COI is when the individual managing the biospecimen resource is also a researcher seeking access to biospecimens. In cases where non-financial 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 Website or written materials.

B.11. Biobank Sustainability

Biospecimen resources should consider the creation of a business plan that governs its mission and operations, consistent with its organization's mission, interests, and capabilities. A business plan helps ensure the biospecimen resource's sustainability by documenting its plan for long-term financial, operational and social management [205, 206]. Financial planning should include initial investments to establish the biospecimen resource as well as its infrastructure renewal (i.e., new equipment and service agreements). Costs may partially be offset by investigator funding when investigators place collections into the custodianship of the biospecimen resource. Additionally, partial funding may result from cost recovery activities when the biospecimen resource shares specimens and data for research; note that any charges made for samples should be consistent with the

recovery of reasonable costs associated with operation of the biospecimen resource and not to generate undue profit for the biospecimen resource.

Financial sustainability is rarely achieved by cost recovery or investigator funding alone; institutional funding is required to support the biospecimen resource in the long term. Operational sustainability planning includes support of quality management, staff hiring and periodic training, contingency planning for disasters, site safety, and the security of the resource and its collections and data. Social sustainability planning should emphasize accessibility to the biospecimens and data of the biospecimen resource within a framework that maintains transparency and public trust.

To better understand the economics of biobanking, NCI coordinated two studies through a series of comprehensive surveys and the development of a web-based planning tool, the Biobank Economic Modeling Tool (BEMT) [207]. The aim of the BEMT, which has since been retired, was to help users obtain an understanding of the true costs of biobanking and better plan for the associated financial challenges. The BEMT source code remains available through GitHub [207]). The Canadian Tissue Repository Network (CTRNet) created an online calculator for biospecimen user fees based on a biobank's operating costs, resources, and biospecimen accrual rate [208, 209]. Biospecimen resource sustainability models, other than cost recovery, may also be considered to support a biospecimen resource over the long term [210]. For example, biospecimen resources may utilize a collaborative agreement model involving more than one approved funding partner. Incorporating diverse funding strategies, such as partnerships with industry, grants, and fee-for-service models, may enhance financial sustainability. Biobank economic modeling tools have been developed to aid in cost recovery and financial planning for biobanking [208, 211].

A thorough discussion of biobank sustainability is available from the Biobanking and BioMolecular Resources Research Infrastructure (BBMRI) [212].

Biospecimen resources should also plan proactively for any potential losses of funding (see B.12. Legacy and Contingency Plans).

B.12. Legacy and Contingency Plans

A critical part of governance planning for biospecimen resources is preparing for the end of the biospecimen collection phase, the end of the physical infrastructure of the biospecimen resource, and/or the conclusion of funding, whether for a single study or the entire resource. These preparations include legacy plans and contingency plans. Legacy plans address anticipated needs such as the storage and distribution of biospecimens and their associated data after funding of the collection phase ends. Contingency plans include aspects of risk management, such as planning for potential sources of alternative support for biospecimen collection and/or storage alternatives should unexpected issues arise [213, 214]. Repositories should develop proactive legacy and contingency plans that anticipate closure of biospecimen cohorts in part or in total. These plans should include options for specimen transfer, custodianship reassignment, or ethically appropriate disposal, with clear governance oversight (See ISBER Best Practices, 5th Edition, Sections A1.2, A3.2, and K4.4–K4.6 for guidance on repository closure, transfer, and legacy planning)[214].

A biospecimen resource's legacy and contingency plans should be formally documented in the governance plans and included in SOPs and quality management plans, coordinated with institutional risk management strategies, and be subject to periodic review and maintenance. A biospecimen resource's plan and policies related to sample disposition and transfer should be designed to maximize biospecimen utility and the information that can be derived from their use, while adhering to the ethical guidelines and regulatory policies under which the biospecimens and associated data were collected and stored. Periodic review should include any changes due to updated local, federal, and international regulations pertaining to human subjects research (see Section C.3.2. Quality Assurance/Quality Control (QA/QC)), which may differ from the regulations in place at the time of collection. Evolving privacy risks due to integration with other datasets [148] and tracking of events such as a participant's decision to withdraw from a study should be reflected in legacy planning. Planning for decision making about the disposition of stored samples and associated data in a biospecimen resource's collections can include outlining potential actions such as the relocation or transfer of all or a portion

of the resource to another approved facility, an effort to anonymize samples and associated data by removing all identifiers and destroying linkage keys (see Sections C.2.8.4. Biospecimen Identifiers and C.6.1.2. Identifiers), the transfer of custodianship and stewardship of the biospecimens for other research needs in accordance with the terms of the informed consent, or, if necessary and permissible, a planful destruction of the biospecimens and associated data.

Multiple stakeholders, including the following individuals and entities, may have a vested interest in the plans and policies related to sample disposition and transfer:

- The study participants who provided the samples and/or their communities.
- The Principal Investigator (PI) of the protocol under which the samples were collected and/or the current PI.
- Institutional collaborators, co-investigators, supervisors and trainees of the PI who may have been involved in study design, collection, and/or use of the samples.
- Government entities, foundations or sponsors who provided funding for the scientific research needs.
- Institutional leadership, for example, the Dean's office or the Sponsored Research Office.
- Other institutional centers and departments that may be interested in using or storing the biospecimen resource.
- The IRB or research ethics board (REB).
- Steering committee(s) for specific studies or biospecimen collections.
- Data protection officers or privacy officers if identifiable information is still retained.

Research participants entrust their biospecimens and associated data to investigators and biospecimen resources to support scientific research, and their donations should be treated respectfully. Investigators have an ethical obligation to be responsible stewards of human biospecimens and data, even when biospecimens and data may no longer be scientifically valuable or financially sustainable. The disposition of 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 B.5. Informed Consent). Community engagement or consultation should be conducted as appropriate (see Section B.3. Engagement of Patients, Providers, and Communities).

B.12.1. Events Leading to Decisions for Disposition of Biospecimens and Associated Data

Legacy and contingency plans should proactively address the handling and disposition of biospecimens and associated data when one or more of the following events occurs: (1) loss or change of institutional leadership or change in institutional priorities, (2) loss of Principal Investigator or other primary steward due to relocation or other reasons, (3) depletion or loss of funding, (4) accomplishment of the specific research objectives of the study, and/or achievement of critical data endpoints, (5) depletion of all or a significant portion of biospecimens, (6) discontinuation of participation by research participants, (7) finding biospecimens of unknown provenance and/or quality, and (8) additional events that may require a change in disposition approach. These potential circumstances are discussed in greater detail below.

B.12.1.1 Loss or Change in Leadership or Shift in Institutional Priorities

Biospecimen resources may face a predicted or sudden change in leadership or shift in institutional priorities that threatens the sustainability of the resource or some of its collections and precipitates a need for action. A change in a lead investigator/PI may be due to a job change or relocation to a different institution, retirement, incapacitation, or death. Institutional priorities may change due to a shift in emphasis in the institution's research portfolio, a lack of researchers at the institution with sufficient knowledge, expertise and interest in the specific scientific field to act as a qualified steward, or a change in funding or funding

level of the institution's physical facilities. Such circumstances require either the identification of a new leader at the same institution, a decision to relocate the resource to another entity, or alternatively, planful and respectful destruction of the biospecimen collection. Consideration of and planning for these challenges should seek the views of the IRB and research participants or other community stakeholders as appropriate and when possible (see Section B.3. Engagement of Stakeholder Communities). Ideally, such challenges will be anticipated and planned for within the governance plan.

The legacy plan should include the following information to prepare for the circumstances where the biospecimen resource PI or leadership is changed, or the priorities of the institution exclude maintaining the resource, including:

- A clearly defined plan for interim leadership and decision-making processes. Leadership may be sought from stakeholders or external entities (e.g., steering committees, IRBs).
- An organizational chart, including a description of the roles (e.g., job descriptions) reporting to newly assigned leadership until new permanent leadership and roles are assigned.
- Alternative storage conditions that could be employed, as well as alternative sources of funding for existing facilities, and/or alternative facilities to which samples could potentially be transferred.

B.12.1.2. Loss or Depletion of Funding

Biospecimen resources may face anticipated or sudden, unexpected loss in funding that threatens the viability of the resource and precipitates a need for a major change. The legacy plan should include contingencies for those circumstances, including:

- A commitment to temporary or bridge funding until final disposition plans can be made. This may include a commitment from the department or institution, e.g., applying for emergency operational funding.
- A description of how existing core funding will sustain the transfer of the biospecimen collection in the event of closure. This may include a plan to earmark some of the existing core funding for a contingency plan or to create an agreement with new transferee groups.
- A conceptual or detailed outline of potential partnerships or funders who could assume custodianship.

B.12.1.3. Accomplishment of the Specific Research Objectives of the Study or Achievement of Critical Data End Points

Completion of study research objectives does not necessarily signify that biospecimens and related data are no longer of value; however, future use should be governed by permissions put in place in the informed consent [213]. Institutions should budget to maintain sample availability beyond primary study objectives. Biospecimen management planning beyond immediate use in the current study should include provisions for enabling reproduction of the original study findings and establishing certain thresholds, particularly in biomarker discovery and validation, by using same-sample derivatives to demonstrate clinical and analytical validity as well as clinical utility [215]. Studies may extend to sharing specimens with collaborating institutions to show cross-platform correlations and/or validation of performance characteristics for research tests lacking standardization. Biospecimens and associated data from clinical trials may be useful in secondary correlative studies beyond the scope of the initial study protocol [169]. These uses may not be apparent until after results are disclosed, and it may become necessary to budget additional funds for maintaining specimens within a set time frame under an institutional policy beyond completion of original study objectives.

Planning for specimen usage after initial study objectives are completed should consider not only primary aims but also reasonably related study objectives that will or might be pursued in the future. Such potential future secondary use of biospecimens should be communicated to research participants during the consenting process and stated in the informed consent document (see Section B.5.3.4. Future Research).

B.12.1.4. Biospecimens of Unknown Provenance and/or Unknown or Poor Quality

In biospecimen resources that have been in operation for a significant amount of time, as well as in ones where storage units and freezers are shared by more than one investigator or group, there is often a good chance that biospecimens of unknown provenance will be found in storage, whether they be individual boxes or entire freezers. Such biospecimens may or may not have associated clinical data and/or collection, processing and storage data; consent documentation may or may not be present [216]; information about the PI and protocol may or may not be available or known; and/or there may be no inventory records that describe the stored biospecimens. It is also possible that biospecimens will be obviously of questionable or poor quality due to such factors as compromised storage conditions (e.g., known freezer failure or visual appearance of melted embedding medium), visual signs of damage to specimens (e.g., FFPE blocks damaged by mice or insects), or obvious inconsistencies in associated data (e.g., wide variations in the presence, legibility, or completeness of accompanying written records).

Biospecimen resources should consider that the research value of such specimens is greatly diminished without knowledge of the study protocol, associated consent permissions and restrictions or other regulatory requirements that may apply, and associated annotation regarding specimen type, disease, and known conditions of collection and storage. Actions may include 1) documenting the existing conditions and available annotation, 2) considering any potential usefulness of the specimens, 3) asking the IRB if the biospecimens can be anonymized for use if sufficient information is available that suggests there is some usefulness of the biospecimens, for example, in method development or assay validation, and/or 4) destroying the biospecimens. Targets to cull the collection may include, for example, samples that are not connected to associated data, for which there is no understanding of the consent under which the samples were collected, or where there are documented sample quality issues. A useful framework that may help biospecimen resources to evaluate the value of their collections has been recently published [217].

B.12.2. Preparation for Disposition Decisions

Regardless of the reason for disposing of a biospecimen resource, specific information should be gathered in order to make sound decisions, some of which are listed below [214, 218].

- Identification of the individuals required to make disposition decisions (e.g., the PI, department chair, IRB, dean's office, and/or committee).
- Assessment of the protocol under which the biospecimens were collected.
    - Original IRB protocol language related to legacy planning.
    - The permissions and restrictions of the informed consent(s) signed by participants (the versions may have changed over the course of the project).
- Any other information about the decision-making process, if available, from the planning and operational stages of the study from which the biospecimens and associated data were derived.
- Documentation of SOPs under which the samples were collected.
- Complete inventory assessment of biospecimens and associated annotation, including:
    - Biospecimen quality and quantity metrics.
    - Review of any catastrophic events in the biospecimen resource that may affect downstream use, such as power outages and freezer failures.
- Preparation and quality check of associated data, including:
    - Preanalytical factors.
    - Clinical data.
    - Laboratory data.

- The potential research value of the remaining stored biospecimens (e.g., uniqueness, rarity, longitudinal collections, quantity and quality of annotation, length of follow-up data).
- The costs and the resources (e.g., staff, freezer space) needed to maintain the biospecimens.
- A list and details of required tasks and personnel/type of role needed for each of the following:
  - Consent assessment.
  - Inventory assessment.
  - Quality assessment.
  - Biospecimen transfer processes.
  - Risk assessment (to include potential for data and privacy/confidentiality breaches as well as biosafety risks associated with sample transfers).

B.12.3. Considerations Prior to Accepting a Collection

Biospecimen resources should consider the following prior to accepting a legacy collection:

- Whether there is a scientific need for the collection to be maintained, and stakeholders who could make use of the collection.
- Whether only part of the collection, rather than the entire collection, represents the most value.
- Whether there are existing resources sufficient for operational management of the acquired collection, including:
  - Long-term funding for the collection.
  - Storage space for the collection.
  - Whether the label type and content are adequate and compliant with regulations.
  - Availability of appropriate staff.
  - A data migration plan, including data quality and mapping/harmonization of data elements.
  - Consideration of whether maintaining the link to identifiers or anonymization is appropriate.
- Transition of governance, including:
  - Establishment of new governance.
  - Whether there will be a role of prior governance in future decisions.
  - Types of research for which materials are allowed and not allowed to be used.
  - Decision-making process for sharing the materials.
  - Sharing with end-users under terms consistent with consent status and institutional policies and under an MTA addressing these requirements (See also Section B.9.1. Material Transfer Agreements).

C. Technical and Operational Best Practices

C.1. Biospecimen Resource Management and Operations

Daily and long-term responsibilities essential for efficient biospecimen resource management and operations can be complex and include organizational considerations, space planning and functional design, resource development, evaluation and solidification of infrastructure requirements, ongoing risk assessment, constant and consistent review of operational issues, and regular resource evaluation [214]. Coordinated management of all of these factors can dramatically improve success in managing and operating a high-quality, highly utilized, and valuable resource.

C.1.1. Organizational Overview of the Biospecimen Resource

An organizational overview document or set of documents can help a biospecimen resource in defining the institutional structural components within and around the biospecimen resource. An overview typically begins with a description of the organizational mandate; associated goals, mission, and vision; operational scope; and core areas of research support (See also the ISBER Best Practices, 5th Edition, Section A2.1 on Repository Governance [214] and ISO 20387:2018, Section 5.1 on General Requirements for Structure [218] and [219, 220]).

C.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. This practice supports transparent governance and aligns with recommendations from the OECD Guidelines on Human Biobanks and Genetic Research Databases [221] and Section A2.2 of the 5th Edition of the ISBER Best Practices [214].

C.1.1.2. Organizational Chart

The organizational chart can be a significant tool in supporting existing governance structures through the 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 it with every new staff member as part of the orientation process, reviewing the current management of the institution (Appendix 3).
- Regular updates to the organizational chart are recommended to reflect changes in leadership or governance.

C.1.2. Biospecimen Resource Personnel, Teams, and Committees

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 C.1.2.1. Related Personnel Descriptions, Teams, and Roles). To ensure the collection of high-quality biospecimens for research, personnel should be well-qualified and trained to adhere to applicable SOPs [218]. See the NCI Biorepositories and Biospecimen Research Branch (BBRB) Website [222] and the NCI Biospecimen Research Database [223] for examples of SOPs that have been contributed by organizations across the world and can be adapted by biospecimen resources for their own applications [7]. ISBER provides a list of educational opportunities and programs by country [224] and offers a course on

biobanking essentials developed in conjunction with the Canadian Tissue Repository Network (CTRNet) [225, 226]. Additional training and SOPs may be required that are specific to the particular study protocols to which the biospecimen resource is contributing.

Updated training of personnel should be conducted on a periodic basis, in accordance with applicable regulations and position descriptions [214, 218]. 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. It is important that a pathologist determines which biospecimen, or portion thereof, is necessary for complete medical evaluation and which is excess (remnant tissue) that may be provided to the biospecimen resource for research purposes. In alignment with CAP recommendations, the involvement of a pathologist for the clinical oversight of tissue release is crucial to ensure that patient care is not compromised. Maintaining chain-of-custody records and integrating pathology review into digital tracking systems can further support traceability and quality control.

C.1.2.1. Related Personnel Descriptions, Teams, 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. Research participants, patient advocates, and community representatives may also be considered key stakeholders. See also Sections B.3. Engagement of Stakeholder Communities and B.4. Transparency and Communication.
- Biospecimen Resource Management Team: Typically consists of a director, associate director, technical director, and director of quality management. Depending on resource size and scope, a compliance officer or designated regulatory specialist may also be included.
- Adjunct Research Support Teams: May include clinical research coordinators and study nurses, research assistants, laboratory technicians, bioinformatics professionals, clinical residents and fellows, and statisticians.
- Internal Support System: May include space planning, financial administration, comptroller, purchasing, environmental services/maintenance, telecommunications, informatics, and marketing.
- External Support/Outsourced Roles: May include vendors, consultants, contractors, architects, and engineers. External personnel/vendors should adhere to institutional data sharing and biosafety policies and comply with ISO 20387:2018 [218].

C.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 interest (Section B.10. Conflict of Interest) 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.
- Community Advisory Board: Provides input on biospecimen resource management and operations from the perspective of patients, research participants, patient advocates, and the local community; for example, see [227]. See also Sections B.3. Engagement of Stakeholder Communities and B.4. Transparency and Communication.
- Biospecimen Use (or Access) Committee: Supports access to biospecimens for research through assessment of criteria such as scientific rationale, validity of the scientific project, regulatory

adherence, potential conflicts of interest, and fair biospecimen/data allocation practices. (See also: B.8. Access to Biospecimens and Data and ISBER 5th Edition [214]).

C.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 are not limited to, the following:

- Office of Regulatory Affairs: Typically established to aid regulatory review and oversight of research protocols.
- Office of Human Subjects Research: Typically performs an auditing function for clinical research trials and related research support centers.
- Office of Research Services: Grant management support and assistance with contract development.
- Technology and Materials Transfer Office: Assists with MTA development and management. See also Section B.9.1. Material Transfer Agreements.
- Legal Affairs: Offers guidance on relevant case law and aids in contractual negotiations and/or disputes.
- Office of Environmental Health and Radiation Safety: Provides guidance and oversight on biosafety but may also consult concerning resource development and/or expansion.

Integrated collaboration with data privacy officers and information security teams may also be required or recommended, in light of increasing digital governance complexity [214].

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 IRB.

C.1.3. Considerations Related to Planning and Development

Consideration of the biospecimen resource mission, operational scope, and objectives is crucial in the execution of all stages of the planning process (See Section B. Governance). For startup resources, initial operational planning and developmental considerations should aim to include the establishment of a business plan that includes a governance structure as well as the development of related policies and regulatory and procedural standards. Once the foundation for governance is set in place, operational procedures such as biobanking protocols, procedures, and formal business development may be developed and/or finalized if already in progress. For biospecimen resources that function as core facilities and/or service providers, business planning may include financial and cost-recovery modeling (see Section B.11. Biobank Sustainability). Established biospecimen resources may wish to revisit their business plans as information about biobanking economics continues to grow, particularly to address any operational disparities in an effort to support best practices and promote long-term sustainability [228-233]. Notably, publicly funded biobanks may consider patient health gains as a return on investment fund expenditures [234, 235]. Also see Section B.11. Biobank Sustainability.

C.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. See also Sections B.2. Roles, Responsibilities and Ownership and C.1.2.2. Oversight Committees.

C.1.3.2. Determination of Procedural and Regulatory Standards

During resource development, it may 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 current best practices and standards documents to determine initial base standards for resource development, operations, management, evaluation, and expansion.
- Orient staff and adjunct teams to current best practice documents and published standards.
- Incorporate best practices and current relevant standards into resource policies, SOPs, and procedures with an emphasis on supporting evidence-based practices [5-9, 223] (Also see Appendix 5. Example of a Biospecimen Evidence-Based Practice). Best practices and standards specific to biobanking include these NCI Best Practices as well as those from the International Society for Biological and Environmental Repositories (ISBER) [10] and the International Organization for Standardization [218]. Standards and guidelines relating to the preanalytical phase are also available from the European Committee for Standardization (CEN)[236] (also listed by SPIDIA4P [237]) and the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM)[238].

C.1.3.3. Business Planning

Business planning can provide justification for financial and institutional commitment, quantification of startup and sustainability costs, and social trust [228-231, 239]. See also Section B.11. Biobank Sustainability.

- Business planning should be a foundational component of biospecimen resource governance and integrated into all aspects of operations, biospecimen resource management, and evaluation.
- Resources should aim to establish and annually update a documented business plan developed with input from leadership, administrative, and technical teams and aligned with the vision and mission of the resource. At the operational level, business plan items should be specific, measurable, actionable, relevant, and time-bound (SMART)[214].
- 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, including cost recovery and fee-for-service models. These should be transparent, compliant with institutional and federal guidelines, and reviewed periodically to ensure financial sustainability [220].

C.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 elements [239, 240]. This includes capital planning, facilities needs assessment, and utility requirements, as outlined in ISBER Best Practices, 5th Edition, Section A5.1: Infrastructure and Facilities [214]. ISBER offers the ISBER Biobank Assessment Tool [241] to help institutions perform evaluative exercises that assess compliance with ISBER Best Practices. Some institutions favor a centralized infrastructure to promote harmonization and achieve standardized, well-annotated, high-quality, robust biospecimen and data repositories. Centralization supports quality control, cost-efficiency, and alignment with FAIR (Findable, Accessible, Interoperable, Reusable) [181] principles for biospecimen data.

Infrastructure requirements can vary based on the biospecimen resource size, type, scope and requirements and may include but are not limited to physical laboratory, office, and adjunct and/or satellite space needs as well as biospecimen tracking and laboratory information management system (LIMS) platforms, additional 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 and cytological preparation.
- Equipment such as chemical and biosafety hoods, centrifuges, liquid nitrogen (LN2) tanks, and freezers.
- Stations for pathology case review and digital pathology image capture.
- 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 digital pathology imaging platforms and other specialized laboratory practices.

C.1.5. Overall Operational Considerations

C.1.5.1. Equipment Selection and Maintenance

Equipment selection complements infrastructure planning and should be considered in parallel with space planning and resource design. The ISBER Best Practices (Section A5.2)[214] and the ISO (Sections 6.4 and 7.5)[218] provide additional information on this topic.

Biospecimen resource management should consider the following when selecting equipment:

- Current resources and budget.
- Current and future services and their need, frequency of use, vendor options, and manufacturing lead time.
- Costs, including the costs of routine energy use and efficiency cost savings, performance, maintenance, lifespan, delivery, warranty, and service contracts, along with current and future service provision options.
- Vendor comparisons (performance specs, delivery timeline, reliability, service record).
- Energy efficiency and sustainability (green lab initiatives).
- 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 may be 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.

C.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. Biospecimen resources may wish to evaluate multiple vendors for equivalency, when possible, to mitigate any impact on business continuity should an unforeseen issue arise, for example, if a vendor needs to be replaced or augmented. The ISBER Best Practices 5th Edition suggests that vendor vetting should include documentation of supply chain integrity and service performance for critical biobanking consumables and equipment [214].

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

Tools such as Gantt charts, project dashboards, or project management software are recommended to facilitate team coordination.

C.1.5.4. Biospecimen Utilization

Biospecimen resources should actively manage the process of biospecimen utilization to promote collaboration and timely research and to honor the gift that participants have made to facilitate research. Also see Section B.8.1. Access to Biospecimens.

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 with the external community through a biospecimen management information system or other means. Examples of information sharing include the following:
    - The NCI Specimen Resource Locator [167], an online repository of basic information about sharable biospecimens (Section C.6.3. Interoperability).
    - The NCTN Biospecimen Catalog [170](See Section B.8.1.5. Availability of Biospecimens).
    - The NIH Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) [242](https://biolincc.nhlbi.nih.gov/home/).
    - The NIH NeuroBioBank [243].
    - The International Repository Locator (IRL) [244].
    - Project- or biobank-specific websites that provide information about available samples, for example, the Genotype-Tissue Expression project (GTEx) collection [245, 246].

C.1.6. Biospecimen Resource Evaluation and Assessment

The evaluation process can be a valuable exercise to aid executive decision-making, with respect to the assessment of future funding needs, overall service quality and effectiveness, customer satisfaction, program results, scientific and financial impact, opportunities for innovation or expansion, crucial lessons learned, and program success. Section A8. of the ISBER Best Practices, 5th Edition [214], emphasizes routine assessment using key performance indicators (KPIs) such as cost-per-specimen, turnaround time, and biospecimen distribution ratios. Such assessment should be done periodically and coordinated with updates to the biospecimen resource's legacy and contingency planning; see B.12. Legacy and Contingency Plans. A useful

framework that may help biospecimen resources to evaluate the value of their collections has been recently published [217].

Biospecimen resource evaluation should include the following general topic areas:

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

Self-auditing and audit preparedness are cornerstones to support and/or evaluate areas of poor performance as well as success in quality of operations. Audits and surveys may be conducted in relation to monitoring end-user support for clinical biobanking efforts [218]. Audit tools are available, including those provided by ISBER [241] and CAP [247](Also see Appendix 6. CAP Accreditation Checklist).

- Self-audits should be documented and occur at regular intervals.
- Findings should inform continuous quality improvement initiatives.
- Resources supporting clinical trials must prepare for both internal and sponsor-driven audits.
- Audit preparedness should include SOP reviews, document traceability, and staff readiness drills.

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

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

Benchmark development should utilize evidence-based metrics, such as utilization rate, cost recovery, and specimen discard rate.

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

Assessing the performance of a biospecimen resource extends beyond financial considerations alone. Formal quantification of performance justifies the benefit, scientific utility, and overall need for the stakeholder's financial investment in the biospecimen resource. In a recent survey of academic, hospital, and government biorepositories, more than half used the following metrics to self-assess performance: the number of samples collected, distributed, and utilized; sample quality; and the number of publications and citations [248]. Some academic biobanks have extended these core parameters to include biobank certification and accreditation and the number of inquiries, supported research grants and projects, research collaborations, supported clinical trials, patents, individuals trained, and research conference presentations [233]. Critically, performance assessment should include measures of input (e.g., operational activity) and output (e.g., scientific contribution and societal impact).

Formal analysis of scientific impact can provide evidence of the inherent and extrinsic scientific value and the contributions of the resource. Proponents of such impact analyses have published guidelines (Biospecimen Resource Impact Factor [249-253]) and developed a model based on the impact of articles utilizing biospecimen cohorts from established biobanks [254]. Some biospecimen resources may not have the financial resources or information they would need to conduct such a self-assessment, except as noted through the ISBER Biobank Assessment Tool (BAT) [241].

Such exercises should, ideally, be performed periodically and coordinated with updates to the biospecimen resource's legacy and contingency planning; see also B.12. Legacy and Contingency Plans.

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

The aim of every biospecimen resource should be to collect, maintain, and disseminate biospecimens and associated data that are of the highest quality required for the intended research use, i.e., fit for purpose.

Considering the rapid pace of scientific discovery and technological advances, it is worth noting that intended research use can be a moving target and future use of biospecimen collections and associated data may require a different level of quality than originally conceived. The highest quality biospecimens are those whose biology most closely resembles the biology of the biospecimen prior to its removal from the research participant. Once collected (and, in some cases, prior to its removal from the body), the biospecimen may begin to take on new characteristics that are artefacts of immediate physical and environmental changes. Changes in exposure to certain nutritional, chemical, or other environmental factors may occur during a surgical or collection procedure, for example, loss of oxygen during surgical clamping (warm ischemia). The biological effects of such changes may continue until biospecimen preservation, when additional artefacts may be introduced [255-268]. The variables introduced in biospecimen collection, processing, and storage procedures, some of which simply cannot be controlled when collecting human specimens, are known as *preanalytical factors* because they can result in inaccurate determinations of the molecular and physical characteristics of the biospecimen during subsequent analysis. The effects of preanalytical factors are reported widely across all types of biospecimens destined for clinical and/or research use. Although not comprehensive of the biospecimen types affected or the effects observed, the following reviews include examples of susceptible analytes and the scope and magnitude of the changes reported in tissue [269, 270], blood [271, 272], plasma [273, 274], cerebrospinal fluid (CSF) [275, 276], saliva [277], urine [278, 279], and feces [280]. Whenever possible, every attempt should be made to minimize the effects of biospecimen handling on biospecimen integrity, and high-quality biospecimens should be the goal.

Biospecimen science is the scientific study of how collection and handling practices affect a biospecimen's quality and the data generated from it. The field of biospecimen science has grown substantially since the *NCI Best Practices for Biospecimen Resources* was first published in 2007. An increase in awareness of both the scope and severity of preanalytical effects has led to a surge in empirical evidence and valuable guidance on aspects of biospecimen handling by well-respected organizations and working groups. Practicality prevents the presentation in this document of a comprehensive review of the field or tailored fit-for-purpose guidance on specimen handling. Rather, highlighted here are examples of preanalytical factors with reported effects on downstream analysis, along with representative corresponding references that may be considered during the planning, documentation, or evaluation of biospecimen handling workflows. Many of the references cited within this document, as well as thousands of additional articles in the field of human biospecimen science, are available in the NCI Biospecimen Research Database (BRD)'s literature repository [223], which supports search capabilities for biospecimen, preanalytical factor, analyte, and assay-specific terms. Each BRD entry includes a tailored summary highlighting preanalytical results and a link to the PubMed abstract when applicable.

Note that the guidance provided in this section is intended for application when planning for biospecimen collection, processing, and storage, prior to the initiation of the collection efforts. Such information may also prove useful when assessing the suitability of retrospectively collected specimens, if details of specimen handling have been recorded. The objectives and practical constraints of each biospecimen collection study will also determine, per specific SOPs, what preanalytical factors can and should be controlled and what data should be collected, as described below.

C.2.1. Determining Which Biospecimens to Collect

The specific mission and goals of a biospecimen resource will influence the type of biospecimens collected. The biospecimens collected should be appropriate and feasible for the clinical setting, as well as appropriate for the downstream applications anticipated for the biospecimen.

If tissue specimens are being collected, they should be reviewed histologically by a qualified histopathologist and qualified for further analysis; this is a requirement for some accrediting agencies [11] (Also see Appendix 6, BAP.02500). The results of histological review can be of critical importance for living patients, should the results provide a conflicting diagnosis from that previously reported, and for downstream analysis. If tumor specimens are being collected, defining tumor content thresholds and histologically verifying that they are met may safeguard resources prior to costly analysis. For example, the NCI's The Cancer Genome Atlas (TCGA)

set a high tumor content criterion (≥ 60% tumor nuclei) to add a measure of standardization to the data generated from 24 different tumor types [281]. In another example, for the NIH's Genotype-Tissue Expression (GTEx) Project, board-certified pathologists evaluated postmortem tissues taken, with the authorization of family members, from 25 or more anatomic sites within an individual donor. Prosection accuracy and degree of necrosis, among other factors, were evaluated and the information was provided to downstream laboratories to inform molecular analysis and overall quality control [113, 115, 171, 172]. In both examples, the goal was to produce authoritative data for the research community; the histological evaluation provided important information to cross-check molecular analysis results and helped to raise the overall level of quality control and, accordingly, the value of the data produced.

Blood biospecimens are more important than ever to collect for biobanking due to the rapid acceleration of research and technologies for analyzing blood and blood products for disease biomarkers. Molecular diagnostic tests utilizing blood samples or "liquid biopsy" are important tools in cancer diagnosis and treatment, with several FDA-approved assays available [282, 283]. Blood samples taken at diagnosis and over the course of cancer treatment can be a critical resource for research, enabling a better understanding of how cancer may respond to treatment. For blood biospecimens, it is generally recommended that the collection tube be chosen based on the potential for analyzing multiple analytes (e.g., DNA, cell-free RNA, proteins).

When biobanking for future unknown use, resources may consider the strategic research needs of collaborating researchers as well as those of the individual institution, be it a specific type of biospecimen, type or stage of cancer, or longitudinal collection. Ideally, biospecimens will be collected to achieve the highest biological quality possible, even when the method of analysis has not been determined *a priori* (See also Section B.11. Biobank Sustainability).

C.2.2. Biospecimen Science Research

NCI has been a leader in sponsoring and conducting systematic studies of biospecimen preanalytical factors and their effects on molecular integrity. NCI programs include the Biospecimen Research Network (BRN) [284, 285] and the Biospecimen Preanalytical Variables (BPV) Program [265, 286]. Research findings from the BRN program improved the understanding of how preanalytical factors during tissue handling, such as warm [256] and cold ischemia [255, 257, 258, 260] and preservation method [255, 256, 260], affect RNA integrity, protein phosphorylation, and gene and protein expression. BRN-sponsored studies also revealed protein- [259] and miRNA-specific [261] effects of delayed blood processing, prolonged frozen storage, and freeze-thaw cycling of plasma and serum specimens.

NCI's BPV Program systematically assessed effects associated with cold ischemia time (delay to fixation) and time in formalin on the molecular profiles of formalin-fixed, paraffin-embedded (FFPE) specimens from several different tumor types that were collected, preserved, and processed using a single set of SOPs -standardized collection across tumor types[287]. Delay to fixation and time in formalin were chosen for study due to previous reports that these were critical preanalytical factors that can vary widely within and between pathology departments and medical institutions. BPV Program findings support limiting cold ischemia time at ambient temperature to ≤ 3 h and the duration of formalin fixation to ≤ 48 h based upon the effects observed on nucleic acid quality [265], array comparative hybridization (aCGH) profiles [267], expression of individual messenger RNA (mRNA) [288], individual small nuclear RNAs [289], and microRNAs (miRNAs) [289], RNA and miRNA sequencing profiles [266], and immunohistochemical staining [268]. The data generated from BPV and the associated clinical information are available for secondary analysis through dbGaP under controlled access.

The current NCI Notice of Funding Opportunity (NOFO) "Integrating Biospecimen Science Approaches into Clinical Assay Development" (PAR-25-325)[290] sponsors biospecimen science research focusing on how the collection, handling, and storage of blood, urine, and biopsy and surgical specimens from multiple tumor types affect the detection of clinically relevant cancer biomarkers. Extramural research funded through NCI's Innovative Molecular Analysis Technologies (IMAT) Program [291] focuses on improving the quality of cancer biospecimens for either research or clinical care through new or improved technologies. These funding

Research in biospecimen science has also been conducted by the global "Blood Profiling Atlas in Cancer (BLOODPAC) Consortium," a collaborator-driven and -funded nonprofit organization. BLOODPAC spearheads collaborative clinical studies aimed at accelerating the development and validation of assays utilizing liquid biopsies [292]. The consortium hosts both the BLOODPAC Data Commons [293], a repository of contributed liquid biopsy data and associated clinical information from multiple studies, and the BLOODPAC Discovery Portal [294], a forum for data files associated with published analysis.

International research initiatives focused on biospecimen science include the **S**tandardisation and improvement of generic Preanalytical tools and procedures for In-vitro DIAgnostics project (SPIDIA) and, more recently, the SPIDIA for Personalized medicine (SPIDIA4P) Consortium [295], both of which were funded by the European Union and coordinated by QIAGEN GmbH in Germany. The aim of these programs was to identify the major questions of biospecimen methodology and preanalytical factors, conduct original research to address these questions, and develop evidence-based practices to guide new biospecimen collections and mitigate preanalytical effects when collecting and utilizing stored biospecimens. SPIDIA4P, along with several other consortia and societies, collaborated to produce 22 preanalytical workflow standards that are biospecimen type-specific, preservation method-specific, and analyte-specific, through the Technical Specifications from the European Committee for Standardization (CEN/TS)[236]; many of these are being adopted by the ISO [237, 296]. The recommendations outlined within these preanalytical standards reflect the expertise of an international technical committee of experts and representative literature evidence in a specific field of study. Guidance contained within preanalytical CEN/TS standards includes but is not limited to the documentation of patient- and specimen-related factors, elements that warrant consideration during the design and verification of preanalytical workflows, and recommendations for specific steps during the preanalytical phase (such as collection, preservation, processing, transport, storage, and quality assessment). The preanalytical CEN/TS standards note that they are applicable for use by medical institutions and laboratories, biomedical research institutions, regulatory authorities, and biobanks.

Collectively, findings from NCI, SPIDIA, and BLOODPAC initiatives have resulted in significant findings that have advanced the field of biospecimen science and promoted best practices for biospecimen use in clinical and basic research programs [255-262, 297-299]. These findings represent an enormous advance for biospecimen science, a field that was barely recognized at the start of NCI's Biospecimen Research Network in 2007.

C.2.3. Biospecimen Science Resources

NCI has also sponsored numerous symposia and workshops to engage clinical, research, biobanking, and regulatory communities in the improvement of biospecimen quality.

These meetings have served to:

- Identify critical preanalytical factors affecting biospecimen integrity.
- Improve the understanding of parameters in the preanalytical workflow that can adversely affect results.
- Identify appropriate quality assessment tools.
- Develop evidence-based strategies to mitigate or prevent the interference of preanalytical effects on existing and new avenues of patient care.
- Identify current knowledge and research gaps [300].

As a service to the research community, NCI also developed and maintains the Biospecimen Research Database (BRD) [223]. The BRD is a well-utilized and critical tool for the research community, supporting NCI's overall effort to improve research reproducibility through evidence-based and harmonized biospecimen procedures. The BRD is a publicly available, online database that includes:

- A literature repository with more than 3,500 expertly curated articles that evaluate potential effects of preanalytical variability on molecular, proteomic, cellular, and morphologic endpoints in human biospecimens.

- The capability to search by details relating to the biospecimen used (patient diagnosis, specimen type, preservative), the preanalytical factor investigated, and the analyte and platform used or by keyword(s), permitting users to identify articles relevant to specific gene/proteins/transcripts, reagents, authors, or assays.
- A highly varied collection of evidence that includes articles sourced from over 750 distinct journals across multiple scientific disciplines.

The BRD literature repository provides the research community with a birds-eye view of biospecimen science literature that may otherwise not come to light. Without this resource, finding biospecimen science literature can be similar to "looking for a needle in a haystack."

To further support the research community and promote the sharing of information that can accelerate cancer research, the BRD also houses a library of over 800 SOPs contributed by more than 100 U.S. Government agencies, non-profit organizations, working groups, and national and international biobanks [223]. The BRD's SOP library addresses two important problems for the scientific community working with biospecimens: a) the lack of detailed biospecimen methodology in primary research articles, and b) the need to learn from others about how they are developing and managing biospecimen procedures for ever-evolving research needs and technical approaches. The goal of the SOP library is to speed up the research process by offering viable SOP options that other reputable organizations or research projects have developed, and to enable the research community to move towards harmonization of procedures.

The BRD SOPs are:

- Version-controlled and citable by a unique URL and identification number,
- Categorized and searchable by topic (ranging from preparation for specimen collection to analysis and storage),
- Downloadable individually or as part of a project compendium.

To date, SOPs from the BRD's library have been downloaded more than 1.7 million times. Organizations may contribute SOPs to the BRD library through the BRD website [223].

The BRD provides the research community with the valuable information they need to determine what methods they should follow for the biospecimen collection, processing, and storage procedures that will support robust and reproducible research at their institution. Ultimately, the BRD's literature and SOP database can improve research reproducibility through increasing transparency of the published biospecimen science literature and established protocols, fostering the development of high-quality and evidence-based protocols, and improving the reporting of critical details of specimen handling.

C.2.4 Factors that Affect Biospecimen Quality

A variety of factors may affect biospecimen quality and research results; these may be divided into two general categories designated "preanalytical factors" and "analytic factors."

- Preanalytical factors refer to collection, processing and storage variations that influence biospecimen integrity prior to its removal from the research participant and carry through to the point at which a biological specimen is ready for testing.
- Analytic factors refer to those variations that affect the performance of a particular testing procedure [301-304].

The *NCI Best Practices for Biospecimen Resources* focuses on preanalytical factors and does not generally address analytic factors.

C.2.4.1. Preanalytical Factors

Preanalytical factors may be divided into three general areas:

- The physiology of the research participant prior to biospecimen collection;
- Biospecimen collection practices; and
- Biospecimen handling practices prior to downstream testing [255-262] (Also see Appendix 5, Example of Biospecimen Evidence-based Practice).

Prior to the collection or removal of biospecimens, a standardized, evidence-based workflow with supporting SOPs should be in place (see Section C.2.6. Role of Evidence-Based Standard Operating Procedures), and a plan should be in place to annotate biospecimens that includes the recording of protocol deviations [214, 218]. Biospecimen annotation should include information about the research participant as noted in Section C.2.4.1.1. Physiology of 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, storage, shipment, etc. [218, 305]. Please see Section C.5. Collecting and Managing Clinical and Epidemiological Data regarding patient clinical data.

Annotation data should be:

- Maintained in a searchable database that can be electronically linked to the biospecimen at all times via a unique identifier or barcode,
- Traceable throughout the biospecimen lifecycle,
- Accessible for clinical and research data integration (see Section C.5. Collecting and Managing Clinical and Epidemiological Data and Section C.6. Biospecimen Resource Informatics: Data Management and Inventory Control and Tracking) [214, 218].

Several resources have been developed by U.S. and international working groups to delineate the data elements for and harmonize biospecimen annotation. The Standard PREanalytical Code (SPREC) represents a comprehensive example of biospecimen documentation that accommodates annotation of the preanalytical conditions of individual biospecimen aliquots and their derivative samples [20-22, 306]. The Biorepository Working Group of the CAP Diagnostic Intelligence and Health Information Technology Committee has released a list of 175 preanalytical data elements that includes those relevant to tissue, blood, and other bodily fluids [307, 308]. The BLOODPAC Consortium has also released minimal technical data elements specific to the preanalytical handling of liquid biopsy specimens [309] and have recently evaluated their overlap with other liquid biopsy best practices, guidelines, and standards [310]. The Biobanking and BioMolecular Resources Research Infrastructure – European Research Infrastructure Consortium [311] has released the third edition of the Minimum Information About Biobank Sharing (MIABIS) terminology, a set of standardized data elements that capture the minimum information required to promote harmonization and enable specimen and data sharing across biobanks [312-315].

The detailed biospecimen collection, processing, and storage procedures utilized for a study is often missing in the scientific literature. The lack of such reporting can contribute to difficulty in reproducing research findings [19]. NCI, with an international committee, published a set of recommendations for reporting the conditions of biospecimen collection, processing, and storage procedures. These recommendations, known as BRISQ (Biospecimen Reporting for Improved Study Quality), have been adopted by several scientific journals and are mentioned in the guidelines for authors for journals including *Nature* [19, 316-318], and are also available through the Enhancing the QUAlity and Transparency Of health Research (equator) Network, a searchable library of reporting guidelines.

C.2.4.1.1. Physiology of the Human Research Participant

Analyte levels may be affected by multiple biological and environmental factors beyond standard demographic variables, such as age, race, and sex [319].

Physiological factors include:

- The overall health [320-322] and diet [323] of the research participant.
- Physiological indicators of health, such as a female's menstrual cycle [324].
- The timing of biospecimen collection relative to time of day [325] and seasonality [326].
- Patient activities such as eating [327], drinking [328, 329], and exercise [330], which can introduce analytical variability for some biofluids.
- The timing of blood collection relative to surgery [331].
- The type of anesthesia administered to the patient [332].

The issue of medications is particularly important as, unless specifically asked, the patient may not remember to disclose over-the-counter medicines (for example, antacids, non-steroidal anti-inflammatory medications, supplements), or drugs that can interfere with biochemical laboratory tests [333]. Importantly, these effects may be interdependent and patient-specific, often presenting as an increase in variability.

Efforts should be made to collect and record information pertaining to participant-related factors to decrease or adjust for the variability of these contributing factors [214, 218].

C.2.4.1.2. Variation in Biospecimen Collection Practices and the Importance of Annotation

Many factors involved in the collection of biospecimens in a clinical setting may be beyond the control of the biospecimen resource, including factors inherent to the prioritization of a patient's medical care. Further, inherent differences in preanalytical workflows between medical institutions can introduce nonconformity that could preclude the direct comparison of biospecimens and their data and can hinder reproducibility and data integration across studies. For example, tissue processing protocols of eleven institutions participating in the Inter-Prostate SPORE Biomarker study differed in the durations and temperatures of fixation, dehydration, clearing, and paraffin infiltration [334], making it difficult to conduct a biomarker validation study across sites. Such challenges in operations and methods may influence the quality of the biospecimens collected and are important to annotate even when beyond control.

Documenting and reporting the details of biospecimen collection workflows are key steps toward ensuring the usefulness of collected biospecimens for future research and improving research reproducibility, as such factors have been shown to affect the quality of both biospecimens (be they tissue, cells, or fluids) and their resultant data. Examples of collection-related preanalytical factors that warrant documentation and standardization within a specimen cohort, when possible, are presented below, along with representative literature evidence. While some steps are common to the preanalytical workflow of both tissue and fluid specimens, such as a delay to preservation, most are unique to a category or specific type of biospecimen; as such, collection-related preanalytical factors for tissue and fluid specimens are discussed separately. Awareness of these critical preanalytical factors can facilitate standardization or harmonization of procedures across sites. Such harmonization can add considerable value to biospecimen collections shared across sites and the data resulting from biospecimen analysis.

C.2.4.1.2.1 Tissue Biospecimens

Typically, tissues and solid tumors can be acquired via biopsy techniques (e.g. fine needle aspiration, core needle biopsy) or via surgical resection. Biopsy techniques typically produce relatively small biospecimens that may impart challenges in obtaining sufficient tissue [335] or tumor fractions [336], which can, in turn, affect DNA [337] and RNA [338] yields and success rates for nucleic acid [339] and proteomic assays [340]. However, while biopsy tissue may be placed immediately into preservative, comparatively larger surgical specimens are vulnerable to increased variation in their exposure to ischemia. During surgical removal of biospecimens, the length of time following the cessation of blood

flow to an organ until its removal from the body (also called warm ischemia time), as well as the length of time it is stored *ex vivo* until its preservation (cold ischemia time), can affect both levels and molecular profiles of target analytes [256, 341-344]; thus, warm and cold ischemia times should be documented when possible [5, 39-41].

With both biopsies and surgical resections, the biospecimen should be preserved as quickly as possible after removal from the patient to minimize cold ischemia time. For example, appropriately sized tissue sections should be snap frozen and/or placed into 10 percent phosphate-buffered formalin or another preservative, as appropriate. The duration [264], temperature [345], and media [346] during cold ischemia should be recorded for individual biospecimens, when feasible, as each has been shown to influence the magnitude of the observed effect. Notably, the effects of cold ischemia are not ubiquitous, but greatly depend upon the analyte [345], the gene/ transcript/ protein of interest [264, 288], and the analytical platform [347] used in the study.

In recent years, alternative fixatives to formalin have been developed and validated. Consideration may be given to non-formalin fixatives, including newer non-toxic, proprietary fixatives and preservation systems. For example, PAXGene Tissue® [5], allows for the preservation of tissue for molecular and histological analysis [348-351]; RNA-stabilizing agents (e.g., RNAlater) that stabilize RNA in tissue and cell specimens are also widely used [348, 352-354]. Biospecimen preservation strategy should anticipate both current and future use cases. Biospecimen resources should consider the tradeoffs of different preservation approaches; for example, some preservatives may not allow for high-quality histological analysis or require alternate analytic approaches. Expected and unforeseen future uses of biospecimens should be considered when deciding on preservation methods. When biospecimens are collected from research participants, the organ site at which the biospecimen is removed (tumor or non-tumor, as well as location within the tumor), any anesthetic used, warm ischemia time (the length of time the specimen is only partially perfused due to vessel ligation during surgery, before complete removal), any stabilizing agents used to preserve the biospecimen following its removal, the type of fixatives used and the length of time the tissues are exposed to fixatives, any further processing, and the temperature at which biospecimens are maintained following collection (as well as duration i.e. cold ischemia time) may all affect molecular stability and degradation. Data describing these conditions should be collected whenever possible as they help to describe the biological state of the biospecimens.

C.2.4.1.2.2 Fluid Biospecimens

Generally speaking, collection-related factors such as the timing and method of collection, type of collection container, and delays to preservation can influence both the quality and analysis of fluid specimens (including blood, urine, saliva, feces, CSF, and other fluids). However, many collection-related preanalytical parameters are defined by the specific type of fluid biospecimen being sampled. For example, clinical chemistry and molecular analytes differed between blood specimens collected (i) from capillaries vs. a vein [355], (ii) a vein using a straight vs. a butterfly needle [356], and (iii) from a vein using different gauges of a straight needle [357]. For urine, the timing of collection relative to voiding (initiation versus midstream)[358] and whether a specimen was collected from the catheter line versus the collection bag [359] have resulted in differences in molecular or cellular endpoints. Further, saliva specimens collected by passive drooling had lower yields of cell-free mitochondrial DNA than those collected with a Salivette® device [360]. For all fluid specimens, the container used for collection should be considered a potential source of variability that should be standardized when possible, as differences in glucose levels were observed between blood specimens that differed in tube type but not tube additives [361, 362] and among CSF specimens that differed in tube (and thus specimen) volume but not tube composition [363].

[5] *Note that the mention of any particular product in this document does not comprise an endorsement by the NCI.*

A delay to freezing or delays in specimen processing steps, e.g., centrifugation, can affect numerous biomarkers in fluid specimens, although effects are often analyte and gene/transcript/protein-specific and the magnitude of the effect often depends on the additives used. For example, the stability of cell-free (cfDNA) and miRNA in plasma is affected by anticoagulant type [364, 365] and the proprietary stabilizer tube used, such as Roche cfDNA®, Streck BCT® or PAXgene blood tubes® [366, 367]. Similarly, the stability of cfDNA in saliva during a room temperature delay can be extended by either adding EDTA or using proprietary tubes [368]. Consequently, for fluid specimens, it is crucial that the method of collection, the collection container, and any additives be validated for the biospecimen type and analytes of interest (See Section C.2.4.1.2.2 Fluid Biospecimens).

Each step in biospecimen handling can potentially affect downstream analytes and, consequently, requires careful consideration. For tissue specimens, processing steps such as fixative type (reviewed in [369, 370]); the temperature and duration of fixation (reviewed in [269, 371]); conditions of clearing, dehydration, and paraffin-embedding (reviewed in [269, 371]) and freezing rate [372] can impact molecular degradation and morphology, although optimal workflows may be dependent on the tissue type [373] and analyte [374] studied. Considerations that are unique to fluid specimens include the method and conditions of transportation to the processing laboratory (for example, by courier or pneumatic tube)[375], tube position (for example, vertical versus horizontal)[363, 376] and centrifugation [360, 377, 378] or filtration protocol [379, 380]. Other critical factors include the size and volume of the biospecimens that will be stored for future use, and the number of aliquots to be prepared from each biospecimen.

The use of multiple small aliquots allows for experimentation, processing controls, and storage of specimens, while minimizing degradation introduced by freeze-thaw cycling of stored samples ([11] (Also See Appendix 6: CAP Biorepository Accreditation Program Checklist, BAP.01900). Additional information on frozen storage and freeze-thaw cycling is provided in Section C.2.8. Biospecimen Storage and in Appendix 6 (BAP.02000) [11].

C.2.4.2. Analytic Factors

When preanalytical factors are introduced, they may lead to differences in the performance of a particular biomarker assay. To minimize errors in research and clinical settings, it's crucial that each assay undergo appropriate analytical validation, the details of which will depend on the purpose of the assay, the type of biomarker assay (integral versus integrated), and the underlying objective [381]. Such validation is critically important for clinical assay reproducibility. When performing analytical validation, the following considerations should be applied:

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

It is also important that the criteria applied during analytical validation reflect those during assay implementation to ensure the assay is, in fact, fit-for-purpose. Optimally, an assay should be validated for each analyte targeted and for the biospecimen type and preanalytical and analytical workflows applied. Validation should reflect intended assay use (e.g., integral vs. integrated biomarkers) and biospecimen-specific conditions. Additional resources on assay validation that may be useful include guidance from ISO [382], the FDA [383], and BLOODPAC [384].

C.2.5. Defining Reference Ranges

Aside from preanalytical and post-analytical factors, research dictates that values for particular cellular and molecular analytes are more accurately represented by a normal biological range of values (or reference range), rather than a single "normal" value, even among individuals characterized as "normal" or "healthy." Disease is often defined as a distinct deviation from this normal range, and the diagnosis of disease depends on knowing the scope of boundaries of normal variation. Where possible, efforts should be made to characterize reference ranges of a population for the analyte of interest, in the intended biospecimen type, under a controlled preanalytical workflow to ensure the likelihood of accurately detecting any deviation from the reference range [385, 386]. Validation of reference intervals for a population using a small patient cohort may also be warranted if differences in patient-related factors are suspected [387]. Of note, the distinction between "normal" and "abnormal" is not always clear, a challenge that was encountered during the NIH GTEx Project [113, 115]. Despite the preferential collection of tissues that appeared "normal" during procurement, from deceased donors whose medical records did not reflect severe illness prior to death, histologic evaluation revealed a small percentage of specimens with evidence of a severe pathological condition (such as pneumonia, cancer, or cirrhosis). Such specimens were excluded from analysis, while specimens with minor and often age-related abnormalities (such as the presence of atherosclerotic plaque) proceeded to molecular analysis. This example demonstrates that "normality" should be defined within the boundaries of a study's scientific objectives and with consideration for the methodology that will be used for analysis. Histological, where applicable, and clinical quality control are necessary to confirm biospecimen suitability for reference population designation and the rationale and criteria used for selecting reference specimens should be documented [214].

C.2.6. Role of Evidence-Based Standard Operating Procedures

To have confidence in research results, it is critical that all reagents be fit-for-purpose and quality-controlled for use in the assay. SOPs should be reproducible with standard reference material (where possible), and control biospecimens that provide a range of anticipated assay values should be utilized; this is a requirement for accrediting organizations [388] (Also See Appendix 6, BAP.01000, BAP.01500).

Assembling and documenting the evidence needed to support SOP development can be a challenging task. NCI has developed a model, the Biospecimen Evidence-Based Practices (BEBPs), for constructing and annotating evidence-based practices. Four documents in the BEBP series have been published [6-9](see Appendix 5 for an example). The BEBPs are publicly available at the NCI BBRB website [5]. Each NCI BEBP document provides fit-for-purpose guidance and includes topic-based summaries of the literature evidence. Appropriate laboratory experts are engaged in the development of BEBPs to provide real-world perspectives, and summaries of pertinent discussions are included.

The CAP Personalized Healthcare Committee formed a Preanalytics for Precision Medicine Project Team that published evidence-based recommendations for key steps in the preanalytical handling of tissue and blood specimens for subsequent molecular analysis [11]. SPIDIA4P is in the process of developing and releasing a set of twenty-two fit-for-purpose preanalytical standards that are based on scientific results and the collective experience of a technical committee of experts in the field. Each preanalytical standard was initially developed as a CEN/TS document, several of which are being adapted as ISO standards to promote consistency and encourage broad implementation [295, 389]. Several scientific societies and their respective committees and working groups are leveraging the expertise of their members to develop guidance for key preanalytical steps. For example, the International Society for Extracellular Vesicles' (EV) subcommittee entitled the Urine Task Force of the Rigor and Standardization released recommendations that include a quick reference card on urinary EV storage [278, 390]; and, the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM)'s Working Group for the Preanalytical Phase have released recommendations for standardizing preanalytical factors and evaluating stability studies [238].

It is currently not feasible to consider the development of assays to measure the stability of every cellular component within a biospecimen. To that effect, protocols that optimize the general stability of biomolecules under certain environmental conditions are recommended [214, 220]. Should a particular biomolecule be of interest, it is important to perform analysis to ensure that the storage and handling conditions implemented will

allow for accurate assessment of that biomolecule, for example, in a biomarker assay. The NCI BRD is a useful resource for surveying the literature for the preliminary assessment of an analyte's susceptibility to a discrete preanalytical factor [223].

C.2.7. Methods Research

All research endeavors should be based on well-characterized and validated assays, whenever possible [391]. Even assays that are exploratory or developmental in nature should be tested to ensure reproducibility and performance consistency over time. "Proof of Performance" tests [305] allow for testing replicate samples over time to allow for the calculation of standard deviations and other measures of assay variability.

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

C.2.8. 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, plasma, CSF, urine, feces, and cells. Individual types of biospecimens should be handled according to SOPs specific to the biospecimen type and the biomolecules to be analyzed—e.g., RNA, DNA, protein, lipid, steroid, metabolite, and morphology—when possible, recognizing that collection in the context of a clinical trial might be constrained by study-specific protocols. Protocols should be revisited periodically for adherence to current best practices, reported literature evidence, and potential changes in future molecular analysis. Although most of the practices in this section assume freezing or chemical fixation of samples, dry or ambient temperature storage procedures may be appropriate for many samples [348, 392, 393].

C.2.8.1. Storage Protocols and Recording Deviations

Standardized protocols should be applied consistently in storing biospecimens to ensure quality and avoid introducing variables into research studies. Biospecimen resource personnel should record storage conditions along with any deviations from SOPs, including information about temperature fluctuations, thaw/refreeze episodes, and equipment failures [305]. 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 (for more information see [214]). Implementing comprehensive data management systems is crucial for tracking biospecimen conditions and ensuring data integrity. Recent literature highlights the role of such systems in maintaining sample quality and facilitating research reproducibility [394].

C.2.8.2. Storage Temperature

Biospecimens should be stored in a stabilized state. As discussed in previous sections, unnecessary thawing and refreezing of frozen biospecimens or frozen samples of biomolecules extracted from the biospecimens should be avoided, and the appropriate size for aliquots and samples should be determined in advance to avoid thawing and refreezing of biospecimens. When samples are stored in a frozen state, the rate at which they are cooled to the desired storage temperature can influence the rate at which molecular degradation occurs, and subsequent freeze-thaw cycles can further degrade the molecular integrity of the biospecimens. Tracking temperature excursions is recommended and may be required by accrediting organizations [388](Also see Appendix 6, BAP.02000). Multiple freeze-thaw events [395] as well as the thaw duration [396] and temperature [397] have been shown to affect molecular endpoints in tissue biospecimens. When thawing/refreezing is necessary, a biospecimen resource should follow consistent and validated protocols to ensure the continued stability of the analytes of interest [398]. Inventory tracking systems should be implemented to minimize disruption of the stable environment during sample retrieval; this is a requirement for accrediting organizations [11, 247](Also See Appendix 6, BAP.02900). The ISBER Best Practices, 5th Edition, recommends regular calibration and maintenance of storage equipment to prevent temperature fluctuations that could compromise specimen integrity [214].

In selecting biospecimen storage temperature, consideration should be given to the biospecimen type, the anticipated duration of storage, the biomolecules of interest, and whether study goals include preserving viable cells [214, 374, 399]. These practices are required by accrediting organizations [11] (Also see Appendix 6, BAP.04200, 04300). Paraffin blocks should be stored at temperatures below 80 °F (27 °C) in an area with pest and humidity control, which is in accordance with ISBER recommendations [214]. Storage of FFPE blocks in areas above the ambient temperature specified [400] or with humidity fluctuations [401] has been shown to seriously compromise nucleic acid integrity and the expression of certain antigens when evaluated by immunohistochemistry. Similar adverse effects of warm temperatures (> 80 °F) [402] and a humid storage environment [403, 404] have been reported for both nucleic acid integrity and immunohistochemical analyses of FFPE slide-mounted sections. Storage of FFPE slide-mounted sections may be useful for standard hematoxylin and eosin staining but is not considered to be generally useful for molecular analysis due to widely reported short-term instability of molecular analytes.

In the case of liquid biospecimens, such as blood, CSF, urine, ascites, saliva, and feces, consideration should be given to separate components such as plasma or serum before storage, when possible, to preserve each constituent under its optimal condition and decrease the risk of contamination with undesired cellular material. Immediate analysis is preferable when practicable, as degradation may occur during freezing [405] or cryopreservation of isolated cells [406]. Generally, the effects of storage duration are attenuated by freezing. As discussed above, if frozen storage is necessary, liquid biospecimens should be aliquoted to reduce the need for and the effects associated with freeze-thaw cycling [407]. Whole blood (rather than fractionated blood) cryopreservation may be an efficient and cost-effective option for processing viable cells in large-scale studies [374, 408, 409].

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 [410]. Lower storage temperatures and cryoprotectant (such as dimethyl sulfoxide) may be used to maintain viable cells for long periods of time [214]. While colder temperatures for tissue preservation are generally reported to yield superior molecular results (i.e., LN2 or VPLN)[411-413], although optimal cryopreservation methods will depend upon several factors, such as the analyte, gene/transcript/protein, tissue type, and assay used, as well as additional parameters, such as whether morphological preservation is needed and if an embedding medium will be used.

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. Biospecimen resources should be aware that temperature zones also occur in -80 °C ultralow freezers, with temperature differences between zones ranging from 5 to 21 °C, depending on the manufacturer [414]. Regular temperature mapping of the interior of freezers is recommended to ensure uniform temperature throughout the storage unit and is required by accrediting agencies [11](Also see Appendix 6, BAP.08100).

C.2.8.3. Additional Storage Considerations

Storage vessels should be validated for stability under the planned storage conditions [214, 415]. Biospecimen containers should be chosen with analytical goals in mind and evaluated prior to use to ensure that contamination [416-418] or chemical leaching [419, 420] into the biospecimen does not occur. For nucleic acids and proteins, tubes that reduce loss due to binding, such as LoBind® tubes (low-binding tubes) [421], are recommended. Further, tubes should be RNase/DNase-free, and the 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. For long-term storage, screw-cap cryovials are recommended; glass vials or vials with pop-up tops are not suitable for ultra-low temperature or vapor-phase storage [214]. Snap-frozen biospecimens should be wrapped in aluminum foil or placed in commercial storage containers to minimize desiccation [415, 422]. Labeling and barcodes should be printed using inks and materials proven to withstand long-term storage conditions (e.g., −80 °C or LN2

vapor phase). Face shields and appropriate gloves should be worn for worker protection (see Section C.4. Biosafety).

For optimal preservation, formalin-fixed, paraffin-embedded tissue should be stored as blocks rather than pre-cut slides until analysis is imminent because degradation will occur under even the best storage conditions (for reviews see [269, 371]. While some facilities have attempted to preserve the molecular integrity of cut tissue slides by vacuum sealing and cold room storage, this entails considerable cost, and there is little or no controlled data to suggest that this strategy is effective. Moreover, slide storage (even in ambient conditions) is more expensive from a biobanking perspective [423]. 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 [371, 401, 424] and storing the slides frozen [425, 426]. Presently, the benefits of taking extra measures to protect FFPE slides from exposure to moisture during storage are unclear, with positive effects reported by some [371, 427, 428] but not others [429, 430]. Optimal storage conditions might vary according to the final use to which stored sections will be put [269, 371], and empirically determining the optimal storage conditions is recommended. An alternative approach to storing FFPE sections is the collection of thicker (20-30 micron) sections in "curls" that are placed into screw cap tubes, immediately placed on ice, and frozen at -80 °C or in the vapor phase of liquid nitrogen as soon as is practicable.

C.2.8.4. Biospecimen Identifiers

Each biospecimen should have a unique identifier or combination of identifiers that is:

- Firmly affixed to the container.
- Clearly legible and compatible with both human and machine reading.
- Durable under the planned storage conditions (e.g., ultra-low temperature, cryogenic vapor).

Guidance and considerations regarding the design of unique identifiers for biospecimens have been developed by others [166, 214, 431-433]. 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. Strategic organization within storage containers can reduce retrieval time and support automated workflows for distribution, auditing, or QC checks. Additional information related to biospecimen resource informatics best practices can be found in Section C.6. Biospecimen Resource Informatics: Data Management and Inventory Control and Tracking. A well-defined tracking system is a requirement by accrediting agencies [11] (Also see Appendix 6, BAP.02800, 02900). A global unique identifier (GUID) may, where appropriate, facilitate the linking of relevant analytical datasets generated for a research participant and/or specific samples [432]. All other relevant information can theoretically be tied to a GUID, bearing in mind research participant confidentiality, security, and informed consent provisions. To protect participant privacy, IDs/labels used for linking datasets should not contain, or be derived from, any identifying information, such as medical record numbers, initials or birth dates of the participants.

C.2.8.5. Storage Equipment Failure

Automated security alarm systems should be in place to continuously (24 h /7 d a week) monitor the function of storage equipment and should have the capability to warn resource personnel immediately when equipment failure has occurred via SMS, email, audible alarms, and/or central monitoring software. 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; such SOPs should include transfer protocols, chain-of-custody maintenance, weather emergencies, and other disaster recovery/emergency situations [11, 214](Also see Appendix 6, BAP.09200, 09300, 09400).

C.2.8.6. Storage Access

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

C.2.9. Biospecimen Retrieval

Samples should be retrieved from storage according to biospecimen resource SOPs that safeguard sample quality. Ideally, the date and time a sample is retrieved and any temperature deviations or damage experienced by the freezer should be recorded as part of an automated LIMS. Key best practices include:

- Physical security: lockable freezers, locked storage rooms, or card-access areas.
- Access logs: electronic or manual documentation of personnel entries and specimen retrievals.
- Role-based permissions: access should be granted based on roles and responsibilities (e.g., QA staff, lab managers, data personnel).

C.2.10. Shipping Samples

C.2.10.1. Shipping Conditions

C.2.10.1.1. Shipping Refrigerated and Frozen Biospecimens

When seeking to regulate sample temperature during shipping, the shipping time, distance, climate, season, method of transportation, and applicable regulations (see Section C.2.10.3. Regulatory Considerations Related to Shipping), as well as the type of samples and their intended use, should be considered [305, 434]. 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 and expected temperatures (See Table 1 below). Pre-warmed gel packs can maintain a temperature of 22-30 °C for a longer duration during winter months [435]. 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; note that 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 [305]. 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 [305]. Temperature-sensitive material should be handled by a courier with resources to replenish the refrigerant in case of a shipping delay [305]. A simple colorimetric or other constant temperature-measuring device such as a temperature data logger, temperature tag, or smart sensor should be included with biospecimen shipments to indicate the minimum and/or maximum temperature within the shipping container. The use of stabilizers and preservatives may permit the shipment of some specimen types (blood, urine, saliva, stool, tissue) at ambient temperature for some analyte classes, providing a cost-effective alternative to cold chain shipment [436-440]. Additional precautions that can be taken when shipping biospecimens include implementing shipping and receiving SOPs [214, 218], confirming the availability of the receiving institution prior to scheduling biospecimen shipments [441], using a trackable delivery method [214, 218], and using an electronic data logger, where feasible.

Table 1. Recommended Shipping Materials and Temperature Ranges.

Target Temperature	Refrigerant Type	Notes
22–30 °C	Pre-warmed gel packs	For protection during winter months [435]
2–8 °C	Gel packs conditioned at –15 °C or phase-change materials	Refrigerated shipping
≤ –20 °C	Frozen gel packs or eutectic plates	Frozen biospecimens
≤ –70 °C	Dry ice pellets or slabs	Classified as a hazardous substance; follow IATA shipping regulations
≤ –150 °C	LN_2 vapor-phase dry shipper	For long-term molecular stability of temperature-sensitive specimens

C.2.10.1.2. Shipping FFPE and Dried Blood Spots

Paraffin blocks and slides may be shipped at ambient (room) temperature in an insulated package via overnight carrier. The use of insulated, rigid packages/containers is considered important to minimize the effect of temperature fluctuations and to protect the blocks from temperatures higher than 27 °C. There is convincing research that tissues stored in FFPE blocks may rapidly lose antigen expression for certain immunomarkers even when maintained in hospital storage areas at 'room temperature,' which in reality may fluctuate widely in non-temperature-controlled areas [403]. Samples on glass or plastic slides should be cushioned and shipped inside a sturdy (not flexible) outer package. FFPE curls intended for molecular analysis should be shipped cold (approximately 4 °C) in an insulated package. Flat biospecimens, such as dried blood spot (DBS) samples on absorbent pads or cards, may be enclosed in a three-containment system (first, filter paper matrix; second, an envelope to secure the contents; third, a sturdy outer package or commercial envelope)[442]. Desiccant packs can aid in humidity control within the shipping container for sensitive biospecimen mediums [214] such as dried blood spots [442, 443].

Inclusion of a simple maximum temperature indicator in each package and documentation of the maximum temperature upon receipt are recommended.

C.2.10.1.3. Precautions

The number and arrangement of biospecimens per package affect whether the appropriate temperature can be maintained for all biospecimens in the shipment. When too many specimens are packed too tightly or without sufficient refrigerant, temperature gradients may develop that may compromise biospecimen integrity. 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 and when feasible, conditions throughout a critical shipment should be monitored by enclosing a device that records temperature during transport. Packaging volume and refrigerant quantity may be adjusted based on prior validation studies, seasonal changes, and estimated transport delays.

C.2.10.2. Shipping Documentation

C.2.10.2.1. Material Transfer Agreement (MTA)

Before any biospecimen shipment occurs, formal documentation of the transfer in the form of an MTA and requisition from the resource inventory is needed. An MTA or similar agreement (See also Section B.9.1. Material Transfer Agreements and Appendix 4) governs the transfer of research materials and any associated data between two organizations. The MTA governs the rights and obligations of the provider and recipient with respect to the use, handling, intellectual property, and disposition of the materials, and

it should be consistent with all applicable laws, regulations, institutional policies, funding agency requirements, conditions of informed consent, and terms for transfer of those particular materials. The MTA also governs any timelines, commercialization, or third-party transfer of the materials and data (see Section K3 in [214]).

C.2.10.2.2. Shipment Tracking

Biospecimens should be shipped only from an attended, authorized 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 and promptly store the samples and/or proceed immediately to processing, should SOPs so specify. Shipments from and to the biospecimen resource should be tracked in a written or computerized shipping log [214], 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 [214].

Shipping documentation should accompany all shipments. Biospecimen resource personnel should electronically send a shipping manifest, a list of sample identification numbers, and descriptions of samples to the biospecimen recipient with storage and handling instructions, if applicable, 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. Any discrepancies, damage, or condition deviations should be documented and reported immediately to the sender [214]. A questionnaire requesting feedback about the quality of samples received may be enclosed in each shipment for quality management purposes.

In general, the concept and procedures for *chain of custody* should be applied and maintained throughout the shipping process. This includes:

- Tracking biospecimen movement across every handoff.
- Documenting all personnel involved in the packing, transfer, and receipt.
- Maintaining integrity of sample ID linkage and handling conditions.

(See Section C.3. Quality Management and [214, 218]).

C.2.10.3. Regulatory Considerations Related to Shipping

C.2.10.3.1. Laws and Regulations

All biospecimen shipments must comply with applicable local, national, and international laws and regulations governing the transport of biological materials. The ISBER Best Practices, International Air Transport Association (IATA) Dangerous Goods Regulations (DGR) for air transport, and U.S. Department of Transportation (DOT) guidelines for ground shipping of biological specimens [214, 434] are helpful resources to consult 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. See also Section B.9. Intellectual Property and Resource Sharing.

C.2.10.3.2. Potentially Hazardous Samples

Additionally, Occupational Safety and Health Administration (OSHA) regulations on toxic and hazardous substances [444] (29 CFR 1910 Subpart Z) and CDC guidance on shipping potentially infectious biospecimens [445] should be consulted to determine whether a substance requires a biohazard label. Additional safety considerations are enumerated in Section C.4. Biosafety.

C.2.10.4. Training of Staff in Shipping Procedures

Biospecimen resource personnel should be trained to ship samples appropriately. Periodic retraining according to governing regulations should be conducted and documented [214].

C.3. Quality Management

C.3.1. Quality Management System

Biospecimen collection, processing, management, and distribution should be carried out within a quality management system (QMS) that contains documented quality assurance/quality control (QA/QC) policies and SOPs along with a system for performance monitoring, corrective actions, and continuous improvement. Following general QMS recommendations, the QMS should ideally be managed by individuals who are not involved in repository operations; however, this might not be feasible for smaller or less established biospecimen resources. The QMS encompasses the biospecimen resource's QA/QC policies and approaches for ensuring that all programmatic and regulatory requirements are consistently 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; several are mentioned below as resources for designing an appropriate QMS for the biospecimen resource. When a biospecimen resource is considering a quality management program, there are many considerations, for example, if the resource has legal obligations to state and federal laws, the type of resource, and cost.

The following resources may be helpful to the development of a QMS:

- ISBER, the International Society for Biological and Environmental Repositories
  http://www.isber.org
- Good Laboratory Practices
  http://www.oecd.org/chemicalsafety/testing/goodlaboratorypracticeglp.htm
- Clinical Laboratory Improvement Amendment
  http://wwwn.cdc.gov/clia/
- ISO (ISO9001: 2015)
  http://www.iso.org
- U.S. FDA Quality System Regulation, 21 CFR 820
  http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=820

C.3.2. Quality Assurance/Quality Control (QA/QC)

Formalized QA/QC policies should be developed and maintained by biospecimen resources to minimize circumstances that could adversely affect scientific results, ensure the safety of personnel, promote operational efficiency of the resource, and 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 and aligned with intended downstream applications (e.g., diagnostic, genomic, proteomic, clinical trial-related research). QA/QC practices should ensure that accurate, complete, and consistent data accompany biospecimens that are to be analyzed for diagnostic and/or research purposes. Preanalytical factors should be documented and monitored, and standards for diagnostic and research-grade biospecimens should be upheld. The following are key elements for QA/QC implementation and auditing:

- Staff proficiency

  - Clear documentation of staff organization, roles and responsibilities.
  - Initial and ongoing training and competency programs for personnel as appropriate; e.g., training in human subjects protections and privacy regulations such as HIPAA training, safety training, and bloodborne pathogen training.
  - Documentation of training and competency assessments.
  - Routine documentation of staff compliance with policies and procedures.
  - Training in risk mitigation, disaster response, and emergency preparedness (e.g., fire drills, freezer failure response).
- Facility infrastructure and equipment
  - Equipment validation and change control, calibration, maintenance, repair procedures, and documentation of environmental monitoring, e.g., temperature monitoring of freezers/refrigerators.
  - Supplier and vendor management program, including inspection and validation of reagents and other supplies and verification of expiration dates and performance characteristics.
- Biospecimen control and documentation
  - Control/oversight of biospecimen collection, processing, storage, distribution and tracking.
  - Documentation and traceability of biospecimen collection, processing, and tracking, including detailed annotation of preanalytical parameters and chain of custody and audit trails (see Section C.6. Biospecimen Resource Informatics: Data Management and Inventory Control and Tracking).
  - 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.
  - Procedures for document control, including:
    - Version tracking of SOPs.
    - Controlled access to current and archived documents.
  - 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 a record of staff adherence to training schedules.
  - Data quality management (source documentation and electronic records), assessment of reporting system.
  - Supply records.
- Internal audit of the 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 institutional policies and specific informed consent, 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.
  - Processes exist for review and updating at designated time intervals.

C.3.3. Standard Operating Procedures Manual

Each biospecimen resource should develop and maintain a comprehensive set of SOPs that clearly state institutional policies and describe all relevant processes in detail. Additionally, each biospecimen resource should maintain a document control program and policies for governing, modifying, or revising SOPs. 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 and deviations recorded. Current copies of SOPs (SOPs manual) should be stored in designated physical or digital locations and available to personnel at all times. Personnel should review and acknowledge their understanding of new and revised SOPs prior to implementation; reviews and associated trainings should be recorded. Any deviations from approved SOPs should be documented, justified, and reviewed by appropriate supervisory or QA staff. Generally, especially for larger biospecimen resources that have the personnel and budget to support a more comprehensive QMS, an electronic document control system may be implemented, e.g., MasterControl™ [446].

A resource for developing SOPs is the NCI's Biospecimen Research Database's (BRD) SOP library [223](also see Section C.2.3. Biospecimen Science Resources). Notably, artificial intelligence (AI) approaches are being utilized to develop SOPs [447].

C.3.3.1. Contents of the Standard Operating Procedures (SOPs) Manual

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

- *Informed Consent.* Each biospecimen resource should have documentation of the informed consent status for each biospecimen. In addition, procedures for obtaining informed consent and protecting the privacy of identifiable human research participants and confidentiality of data should be clearly described, including HIPAA compliance, as should procedures that follow in the case of withdrawal of consent, including destruction or return of biospecimens and removal from databases, where applicable.
- *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 that purchased supplies are approved, 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, see also Section C.2.8.4. Biospecimen Identifiers.
- *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, preferably in the form of fixed SOPs that may be shared with researchers and/or posted online. This includes detailed descriptions of supplies, equipment, methods, and processing for the division of a biospecimen into multiple aliquots. Biospecimen collection and processing procedures should always include the recording of personnel names, dates, and times to accurately record these potential sources of preanalytical variation.
- *Storage and Retrieval.* Each biospecimen resource should define procedures for the storage conditions, temperature ranges, container organization strategies, and inventory management processes, including real-time tracking and retrieval of biospecimens from a biorepository, processes for adding new biospecimens and withdrawing biospecimens, responding to and filling requests/distribution, and final disposition of biospecimens.
- *Shipping and Receiving.* Each biospecimen resource should have defined procedures and policies for the packaging, labeling, and transportation coordination for both ambient 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; compliance with IATA and hazardous material shipping 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 C.2.10. 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 review and confirmation of histopathology diagnosis; nucleic acid integrity, or biomarker expression and validation; and use of reference standards, replicates, or proficiency panels, if applicable.
- *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 (e.g., SNOMED, ICD-10) (see Standardized Systems for Clinical and Pathology Data under the Web Resources section, and Section C.6. Biospecimen Resource Informatics: Data Management and Inventory Control and Tracking).
- *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 C.4. Biosafety).
- *Training.* Each biospecimen resource should have policies and procedures for initial and ongoing training requirements of all staff members by role. Such training should be documented and include policies and procedures to manage corrective actions; resolve inventory and shipment discrepancies; monitor all sample storage; and 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 [448]. Security SOPs and policies should include information on points of contact and designated backup personnel, including names and emergency contact numbers.

C.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. The effectiveness of QA/QC measures should be evaluated on a routine basis.

C.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 the biospecimen resource personnel who process them, particularly during processing. Consequently, all biospecimens should be treated as biohazards [449]. In addition to taking biosafety precautions, biospecimen resources should adhere to key principles of general laboratory safety and undergo routine biosafety audits and training. See Appendix A of the ISBER Best Practices [214] for additional internet references concerning laboratory and biobank biosafety. Also see the NIH Office of Science Policy's Biosafety and Biosecurity Guidance website [450] and the CDC sixth edition of *Biosafety in Microbiological and Biomedical Laboratories (BMBL)*[451].

C.4.1. Biohazard Precautions

C.4.1.1. Safety Precautions

Laboratories and biospecimen resources should assume that all human specimens are potentially infective and biohazardous [449]. For example, OSHA's Bloodborne Pathogens Standard regulations[444] (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, CSF, dura mater, brain tissue, and other biospecimens should be handled according to standard precautions and labeled according to applicable OSHA requirements. Biospecimen resource work practices should be based on standard precautions similar to those used in laboratories and clinical settings. Two basic safety precautions should be followed in laboratories and biospecimen resources that handle biospecimens: (1) Wash hands frequently, and (2) always use personal protective equipment (PPE), including face protection, gloves and lab coats when handling biospecimens or working within or around freezers and liquid nitrogen tanks [451]. Mechanical pipetting devices should be used; mouth pipetting should be strictly prohibited. Routine surface decontamination and proper waste disposal should also be conducted according to institutional biosafety guidelines. Additional good general laboratory work practices are outlined by Grizzle and Fredenburgh [449] and in the NIH biosafety guidelines [452].

C.4.1.2. Biospecimen Exclusion

A biospecimen resource should establish clear and consistent policies regarding the inclusion or exclusion of biospecimens based on varying levels of biohazard risk. For example, depending on the potential for splash or aerosol exposure, human specimens of unknown infectivity should be handled under biosafety level-2 (BSL-2) conditions, as outlined in the Centers for Disease Control and Prevention (CDC)/NIH booklet "Biosafety in Microbiological and Biomedical Laboratories" (BMBL)[451]. At BSL-2, when biospecimen containers are opened for processing, they should be handled in a certified BSL-2 biological safety cabinet (hood). All biospecimen resources that handle human specimens should operate under the applicable OSHA bloodborne pathogens standard and develop and implement an exposure control plan in accordance with OSHA standards [444] (29 CFR § 1910.1030). Additional precautions should be applied, as outlined in the BMBL. Some activities, such as droplet-based sorting [453], may require higher containment, but in other cases, less stringent practices may be acceptable. Therefore, biospecimen resource staff members should be trained to conduct biosafety risk assessments and determine appropriate levels of containment.

C.4.1.3. Policies

Biospecimen resources should establish policies consistent with the CDC's "Select Agents and Toxins" regulation [454] (42 CFR Part 73), as applicable. This regulation implements provisions of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, establishing 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 serious threat to public health and safety, to animal health, and to animal and agricultural products.

C.4.2. Biosafety Best Practices

C.4.2.1. Requirements

Biospecimen resources should remain up to date with relevant governmental and accrediting agency biosafety requirements, including sources of current information concerning laboratory biosafety for use in developing an overall program in safety and associated training programs (see the CDC/NIH documents referenced in Section C.4.1. Biohazard Precautions).

C.4.2.2. Risks

Biospecimen resources should perform comprehensive risk assessments to identify key biosafety issues associated with routine laboratory activities. Each activity should be analyzed for potential safety issues and appropriate mitigation measures and safety controls should be implemented.

C.4.2.3. Working Guidelines

Written working guidelines should be developed based on Federal and State requirements, institutional experience, and peer-reviewed guidance. These guidelines should be reviewed and updated regularly as needed and revised in response to identified deficiencies or new information.

C.4.2.4. Training

A formal biosafety training program should be developed, implemented, and updated regularly. 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 also include any site- and/or building-specific emergency procedures.

C.4.2.5. Exposure

Biospecimen resources should document all incidents involving potential exposure to biohazards and ensure that appropriate medical evaluation and treatment are made available in a timely manner.

C.4.3. General Laboratory Safety

In addition to biosafety, biospecimen resources should follow general safety regulations and procedures regarding chemical, electrical, fire, physical, and radiological safety (ISBER 2023 Best Practices [214], Section F.4.; OSHA General Industry Standards [455] 29 CFR 1910).

C.5. Collecting and Managing Clinical and Epidemiological Data

Appropriate annotation of biospecimens is crucial to the overall usefulness of the biospecimen resource for scientific research [456, 457]. Biospecimen resources collect and store biospecimens and associated data using multiple methodologies and procedures. The extent of the collection and annotation of associated data may vary greatly depending on scientific need. Researchers rely on banked biospecimens for a wide variety of scientific purposes and use different analysis platforms and technologies. The objectives of their studies may require a great deal of associated clinical and/or epidemiological data to achieve the scientific goals of the study or, alternatively, may require minimal data. Therefore, data recorded by investigators and biospecimen resources

depend on the types of biospecimens collected, study objectives, and the requirements of any envisioned future use.

C.5.1. Regulatory Compliance

Data collection activities should conform to U.S. FDA requirements [458](21 CFR Part 11), if and where applicable, so that the data may be cited and/or used in Investigational New Drug (IND) and Investigational Device Exemption (IDE) applications. Additional regulatory guidance is provided in Sections B. 5. 1 Federal Regulations and Guidelines Pertaining to Informed Consent for Biospecimen Collection and Use; B.7. Privacy and Confidentiality Protections; B.8.2. Access to Associated Clinical and Research Data.

C.5.2. Collecting Clinical and Epidemiological Data

C.5.2.1. Privacy Regulations

As appropriate for the purpose and nature of the biospecimen resource, relevant clinical and/or epidemiological data associated with a biospecimen should be collected in accordance with applicable privacy statutes and regulations, and human subject protection regulations governing the acquisition of biospecimens and associated data (see Sections B.5. Informed Consent and B.7. Privacy and Confidentiality Protections for additional information and references). Clinical and/or epidemiological data associated with the biospecimens should be used and disclosed only for research and development, in compliance, as applicable, with regulations that include HIPAA [81] and HITECH [459], DHHS and FDA human subjects protection regulations (see Section B. 5. 1 Federal Regulations and Guidelines Pertaining to Informed Consent for Biospecimen Collection and Use), and applicable State and local laws.

C.5.2.2 Updates to Data Collection Requirements

If the biospecimen resource is the point of access for associated clinical and/or epidemiological data, the resource should track researchers' requests for specific associated data to guide the refinement of clinical and/or epidemiological data collection, as appropriate, based on the intended purpose of the resource. Summary reports of these requests should be shared with entities responsible for data management to ensure that future collections align with evolving research priorities.

C.5.3. Longitudinal Clinical and Epidemiological Data

C.5.3.1 Data Types

If the study design and objectives require, biospecimen resources should collect and store longitudinal data following applicable informed consent and authorization requirements. Based on these requirements, information linked to biospecimens may include demographic data, lifestyle factors, social determinants of health data [460-462], environmental and occupational exposures history, cancer history, pathology data including histological and imaging data, diagnostic data, information on initial staging procedure, treatment data, social determinants of health data, and any other data relevant to tracking a research participant's clinical outcome (see examples in the Minimal Clinical Data Set, Appendix 1 for basic Common Data Elements (CDEs) that may be considered). Different biospecimen resources may require more or less detailed annotation based on the primary intended research use of the biospecimens. The dataset for clinical and/or epidemiological annotation should be based on the needs of the biospecimen resource users, as well as the overall feasibility of collection, storage, and sharing of the data.

C.5.3.2. Database and Data Access

Databases developed for longitudinal studies should use coded data associated with a biospecimen and 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. The methods for collecting and recording data should be the same across all study sites and consistent over time. To facilitate matching of biospecimens and associated data to participants, each participant should have a unique participant ID that is consistent across all time points or "collection events." Time points should be clearly

defined, for example, before treatment or after treatment. The timing of each data collection point should be consistently recorded and managed. Dates should be de-identified and/or obscured when possible using various methods, such as converting exact dates to times from a reference date, or processing exact age to age ranges (converted to intervals), to reduce re-identification risk (see Section B.7. Privacy and Confidentiality Protections). Policies and protocols should be in place to facilitate access to uniform longitudinal data (e.g., treatment and outcome information, as appropriate) while protecting research participants' privacy and confidentiality.

C.5.3.3. QA/QC

Biospecimen resources should establish a framework that defines policies, standards, roles, and responsibilities for managing data collection to ensure the quality of data. Typical QA/QC steps include data entry checks; range, logic, and consistency checks; outlier analysis; review by data managers and clinical monitors; and periodic audits to verify data accuracy and integrity. All QA/QC activities, including identified issues, corrective actions, and justifications for data discrepancies should be properly documented and comprehensive records maintained. To collect and maintain high-quality longitudinal information, biospecimen resources should establish data quality metrics to monitor the effectiveness of QA/QC activities and identify areas for improvement. Curation of clinical data with validation of the collection process and QA/QC should be conducted by dedicated and trained personnel. For additional information on specimen annotation and quality assurance, see sections C.2.4.1. Preanalytic Factors and C.3.2. Quality Assurance/Quality Control (QA/QC), respectively.

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

Biospecimen resources should have robust, validated information systems in place to ensure accurate biospecimen identification, data integrity, and research participant privacy protection. Such systems may vary in sophistication and functionality to achieve these goals. The use of a minimum set of functional, operational, and legal requirements should be considered best practices (as outlined in this document) and should be taken into account when developing or selecting informatics systems to support biospecimen resources.

For more detail on data sharing, see Section B.8.2. Access to Associated Clinical and Research Data.

C.6.1. Functionality—General

C.6.1.1. Data Types

At the biospecimen resource level, informatics systems should be capable of tracking all phases of biospecimen management from research participant to researcher, including biospecimen acquisition, processing, handling, QA/QC, biospecimen quality measurements (such as RNA Integrity Numbers), inventory, and inventory activities. Such systems should also be able to capture and manage associated clinical data elements that further describe the biospecimens, or, alternatively, link to complementary system(s) performing clinical data collection and storage.

C.6.1.2. Identifiers

Each biospecimen and derivative sample should be assigned a unique ID within the system. The unique IDs may be used to track the biospecimens throughout their lifecycle within the repository. The informatics system should have the capability of linking the labels on the physical biospecimen container (e.g., paper labels, QR codes, or barcodes) to other information regarding that biospecimen in the system. The unique ID should not contain, or be derived from, any identifying information, such as medical record numbers, initials, or birth dates of the participants.

C.6.1.3. Association of Biospecimen Data with Clinical, Epidemiological, and Analytical Data

Informatics systems should be capable of managing clinical and epidemiological data associated with a biospecimen, as described in Section C.5. Collecting and Managing Clinical and Epidemiological Data, and/or link biospecimen data with external sources of such data, where applicable. This capability should enable seamless integration of biospecimen and clinical data for downstream research applications, while maintaining appropriate safeguards for privacy and data access control. Ideally, biospecimens should also be associated with sources of analytical data derived from the biospecimen or derivative sample and/or from the same research participant. The use of global unique identifiers (GUIDs) for the research participant and any derivative samples can facilitate such data connections while maintaining privacy protections [432]. See also Section C.2.8.4. Biospecimen Identifiers.

C.6.1.4. Security

Biospecimen resource informatics systems should provide role- and project-based access control to system functionality and data. The role-based access control (RBAC) should support at least the flat implementation level recommended by the National Institute of Standards and Technology (NIST), and preferably the hierarchical level as well [463]. Project-based security should implement a separate RBAC to guide data access based on project/study/protocol privileges.

Biospecimen resource informatics systems that store PHI and/or personally identifiable information (PII) should adhere to all security regulations for such data (e.g., HIPAA, HITECH). These systems should also meet the criteria for NIST data stored and accessed at the Federal Information Modernization Act (FISMA) moderate level [464].

C.6.1.5. Data and Biospecimen Access Logs

Biospecimen resource informatics systems should maintain vital system statistics and audit logs of all access to PII and PHI and activities associated with biospecimen handling in the database. These logs should include the user identity, date and time stamps, type of access (view/edit/export), and justification for data interaction. Logs should be non-editable, securely stored, and periodically reviewed for compliance and security assurance.

C.6.2. Functionality—Identification and Tracking of Biospecimens

C.6.2.1. Standard Definitions

For informatics purposes, a biospecimen refers to a physically distinct specimen usually stored in a single container. Multiple physical parts created by extraction, division into aliquots, or other physical division of a biospecimen are considered new biospecimens and are referred to as samples in this document and/or referred to as derived (or child) samples. Each sample requires a new unique identifier. The origin of each sample should be recorded. Biospecimen resources should define standard terms for all lineages of biospecimens, from initial collection to subsequent divisions and extractions. Biospecimen resources should employ an existing standard terminology or modify an existing standard to harmonize data elements for semantic interoperability so that the systems can exchange data with other systems with unambiguous and clear meaning [465].

Available guidance on key steps, parameters, temperatures, and durations that should be recorded is detailed in SPREC V4.0 [22]. The BLOODPAC Consortium has released minimal technical data elements specific to the preanalytical phase [309] and have recently evaluated their overlap with other liquid biopsy best practices, guidelines, and standards [310]. Critical annotation that should be included in publications of research results based on the biospecimens is outlined in the BRISQ recommendations [19].

C.6.2.2. Unique Identifiers and Labels

As previously noted, biospecimen resources should employ a method to assign a unique identifier to each biospecimen and derivative and maintain a mapping of the different derivative entities (e.g., aliquots) to the

original identifier for each biospecimen. Global unique identifiers (GUIDs) may aid in linking derived data to a biospecimen and its associated aliquots/derivatives. In addition, when biospecimens and derived samples are shared among biospecimen resources or different research studies, addressing QC questions may rely on having a GUID to provide traceability (see Section C.2.8.4. Biospecimen Identifier). As outlined above, GUIDs can be an important element of linking biospecimens and participants while ensuring the association between a biospecimen, derived samples, and associated data does not expose PII from participants.

Each biospecimen and derived sample should be assigned a unique, non-descriptive, system-generated identifier or combination of identifiers, such as a number and/or barcode, which should not be reflective of its identity (i.e., current storage location position, clinical data, patient identifiers, etc.). For all biospecimens, labels should be printed in both machine-readable and human-readable formats. The label should link back to the inventory management software.

These recommendations are most applicable to prospective biospecimen collections because implementation in existing collections may not be feasible. In this context, the scope within which identifiers are unique applies to an individual system and the biospecimen resources it supports.

An independent Honest Broker mechanism is recommended when the return of results back to patients and/or health care providers is implemented in a study. This mechanism can prevent investigators or other individuals from identifying the patients directly or indirectly but allows research results to be returned appropriately (see Section B.6. Return of Results).

C.6.2.3. Tracking Significant Events

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

C.6.2.4. Position Identification and Updates to Location

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

C.6.2.5. Query Capability

The database system for the biospecimen resource should support various query capabilities to perform functions from data integration to data integrity validation, in addition to data retrieval. This functionality should ideally support both operational workflows and research-specific data needs, including custom reports, advanced filtering, and export options.

C.6.2.6. Audit Trail

The biospecimen resource database should maintain a secure, tamper-proof audit trail capability to maintain records on all changes made to the data, including but not limited to all biospecimen and derivative sample data, system metadata, and clinical data. The computer-generated and automatic reports should include the following: original data and new data; date and time changed; how the changes were made; who made the changes; and why the changes were made.

C.6.2.7. Annotation

Since a biospecimen resource may track samples from many different studies or from different collections, and to achieve efficient data management at the biospecimen resource, consideration should be given to what level of detail the inventory management system can and is needed to contain vs. what should be stored in an external database and linked to the inventory via a unique identifier. Consideration should be given to storing confidential patient clinical information separately from inventory data, such as sample information and location.

The informatics system may also be designed to handle digitally scanned documents related to the sample. Relevant documents may include pathology reports, clinical lab test results, donor consent forms, MTAs, or the necessary institutional permit or shipping documentation. These documents should be securely stored and indexed to allow controlled access by authorized users, supporting regulatory and operational needs.

C.6.3. Interoperability

C.6.3.1. General

Although biospecimen resources may have different informatics requirements and systems based on their unique workflows and operational models, these systems should be interoperable when feasible to enable the integration of clinical and research data, the establishment of distributed biospecimen resources, and the enhancement of scalability for multi-site collaboration. The adoption of Common Data Elements (CDEs) for inventory and clinical data, for example, can facilitate integration with research data. Such interoperability should enable integration with local systems and authorized external systems.

C.6.3.2. Data Standards

The informatics systems should implement established data standards where possible and ensure data is structured and formatted in a way that is universally understandable (ISO, [218]; Minimum Information About Biobank Data Sharing (MIABIS), [466]). The use of CDEs for inventory and clinical data facilitates harmonization, data interoperability, and compatibility with broader research ecosystems. Interoperable systems should support integration with both local institutional databases and authorized external platforms. Even if the informatics systems utilize non-standard data elements for storage internally, the system design should allow for configurable translations to one or more established standards. When needed, new data standards can be developed based on existing or custom schemas, ontologies, vocabularies, or protocols. Data standards may evolve over time and biospecimen resources may need to keep pace with evolving standards.

NIH resources are available to support data standards. The NIH Common Data Element (CDE) Repository [467] includes openly available, expert-vetted/endorsed CDEs and individual sets of CDEs/Forms that were implemented in NIH-funded programs/studies and may be used as resources to create new CDEs to meet individual project needs. A set of vocabulary standards and mapping tools to transform heterogeneous data into harmonized common data elements to improve interoperability, along with terminology tools for Health Data and Health IT, are developed and maintained at NLM/NIH [468]. NCI's Cancer Data Standards Registry and Repository (caDSR) provides a comprehensive resource consisting of database, APIs, and web-based tools for creating and using data standards for biomedical research, including cancer [469].

C.6.3.3 Governance

The informatics systems should follow an appropriate governance framework that supports data standardization, access controls, and management to facilitate data sharing and discoverability as well as to protect the identity of research participants. It should be a top priority that data management meets

regulations and quality standards (See Sections B.7.2. Federal Regulations Pertaining to Privacy and B.7.3.5. Data Access System).

C.6.3.4. Interface

Data systems should ideally provide a published, documented, and accessible application programming interface (API) for other systems to interact with. Changes to this interface should remain backward compatible as much as possible in order to minimize disruption to connecting systems. The API implementation should include both automated conformance and interoperability testing to ensure robustness. APIs should be developed with long-term sustainability and reliability in mind, enabling seamless interaction with both internal and third-party systems.

C.6.3.5. Security

Interoperability APIs should support a security layer at least as secure as other system interfaces. The API should enforce all institutional business and security rules on connecting systems and provide controlled access for authorized users only. Evaluation of the system's API should be measured against NIST guidelines, i.e. the NIST Special Publication 800-30, Guide for Conducting Risk Assessments [155].

C.6.3.6. Data Sharing

Biospecimen resource informatics systems should ideally be capable of sharing appropriate, de-identified biospecimen data to users at remote locations for multiple purposes, including satisfying reporting and regulatory requirements as well as searching for potential biospecimens for a proposed scientific study. All shared data should comply with applicable data use, privacy, and consent restrictions. See Section B.8. Access to Biospecimens and Data for more information on data and resource sharing.

C.6.4. Selection of Biospecimen Resource Informatics Systems

C.6.4.1. Organizational Requirements

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

C.6.4.2. Technical Requirements

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

- Performance requirements (speed, uptime, responsiveness).
- Security requirements (encryption, access control).
- Usability and scalability requirements (user-friendly interface, support for growth).
- External interface and system connectivity requirements (e.g., APIs, interoperability).
- Compatibility, portability requirements (cross-platform, cloud/on-premise options).
- Maintainability requirements.

Common requirements to gather and evaluate include: biospecimen tracking, biospecimen processing and history, data entry, data verification, querying and reporting, ID/GUID assignment and relationships, label printing/scanning, audit trails, interoperability, security, scalability, validation and implementation requirements, infrastructure requirements, IT support requirements, number of users, regulatory compliance (e.g., HIPAA, 21 CFR Part 11), cost for purchase and maintenance.

C.6.4.3 Information Systems Evaluations

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

As part of the evaluations, an assessment of the system provider should be performed for their capability to provide implementation, training resources, support, and ongoing maintenance within budget.

C.6.4.4 Build versus Buy

The determination of "Build versus Buy" is complex with many considerations of resources, personnel, schedules, budgets, politics, and organizational capabilities. Building a customized system may allow the biospecimen resource to meet the operational and workflow requirements in every respect, but requires resources, funding, and a commitment to ongoing maintenance. Purchasing a system allows the biospecimen resource to take advantage of existing technology at a potentially reduced cost and implementation timeline, but with functionality that may not precisely map to the original needs. There is no standard answer to this question; individual biospecimen resources must weigh the trade-off between the flexibility of building custom software versus the faster implementation and potential cost savings of purchasing a pre-built solution and make a strategic decision on the best path forward for the organization.

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

C.6.5.1. Dependability

Biospecimen resource informatics systems should have an operational infrastructure to support continuous and secure operational access, ideally 24 hours a day, 7 days a week, within a monitored and physically protected environment.

C.6.5.2. Disaster Recovery

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

C.6.5.3. Quality Control

Biospecimen resource informatics systems should be periodically evaluated to ensure that the system meets best practices criteria and the latest operational needs of the biospecimen resource. Random quality control checks should be performed on the physical inventory, confirming that the physical location of stored biospecimens matches that provided in the informatics system. All system tools and methods should be validated to ensure their accuracy in performing that task and include documented corrective actions for any discrepancies found.

C.6.5.4. Physical Security

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

C.6.5.5 Software System Validation

Initial validation of the informatics system should be well-documented to ensure data integrity, accurate process workflow, and adequate audit trail. Regulations such as the FDA's 21 CFR Part 11 dictate requirements to include in the validation plan [470].

A detailed written validation plan should identify areas with the potential for high risk in the software and how such areas will be thoroughly tested and then mitigated. Particularly susceptible areas are data migration points, data flow junctures, system configurable areas, and any customized features.

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

Subsequent validation of each upgrade to the system should replicate a portion of the initial validation in a non-production (test) environment, to prevent unidentified regression errors as well as a full validation of the upgraded portion of the system.

C.6.6. Regulatory Issues Pertaining to Informatics Systems

Besides those issues identified in Section B. Governance, the following regulatory issues should be addressed as applicable.

C.6.6.1. Regulations

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

- Applicable State and Federal Regulations.
- Data Privacy Protection.
- 508 Compliance *(limited to Federal Government-sponsored systems)*.
- Security Regulations (e.g., FISMA).

C.6.6.2. Security

Biospecimen resources should refer to the NIST Special Publication 800-30 Guide for Conducting Risk Assessments [471], as applicable, to determine the appropriate level of security for informatics systems.55

C.6.6.3. HIPAA/HITECH

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

C.6.6.4 Review and Updates

Periodic review and updates to the informatics system(s) are recommended to accommodate emerging technologies, new research needs, and evolving regulatory standards.

WEB RESOURCES

Biological Material Transfer Agreement

MTA for Human Materials,
NIH Technology Transfer
National Institutes of Health
https://www.techtransfer.nih.gov/partnerships/forms-model-agreements#MTACTA

Uniform Biological Material Transfer Agreement
Federal Register
https://www.federalregister.gov/documents/1995/03/08/95-5644/uniform-biological-material-transfer-agreement-discussion-of-public-comments-received-publication-of

Code of Federal Regulations

US Government Information (GovInfo)
https://www.govinfo.gov/app/collection/cfr/

Conflict of Interest

Financial Conflict of Interest,
Grants and Funding
National Institutes of Health
https://grants.nih.gov/policy-and-compliance/policy-topics/fcoi

Managing Conflicts of Interests and the Introduction of Bias, NIH policy Manual Section 2400-04
National Institutes of Health
https://policymanual.nih.gov/2400-04

Electronic Records and Electronic Signatures

Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations: Questions and Answers
U.S. Food and Drug Administration
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electronic-systems-electronic-records-and-electronic-signatures-clinical-investigations-questions

Health Information Portability and Accountability Act of 1996

Security Rule and HIPAA for Professionals
Department of Health and Human Services
https://www.hhs.gov/hipaa/for-professionals/index.html

Human Subjects Regulations

Office for Human Research Protections
Department of Health and Human Services
https://www.hhs.gov/ohrp/index.html

Exempt Research and Research That May Undergo Expedited Review
Office for Human Research Protections
Department of Health and Human Services

[6] All listed Websites were accessed on April 2, 2025.

https://www.hhs.gov/ohrp/regulations-and-policy/guidance/exempt-research-and-research-expedited-review/index.html

Frequently Asked Questions
Office for Human Research Protections
Department of Health and Human Services
https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/index.html

The Genetic Information Nondiscrimination Act of 2008: "GINA"
Department of Labor
https://www.dol.gov/agencies/oasam/centers-offices/civil-rights-center/statutes/genetic-information-nondiscrimination-act-of-2008/guidance

National Human Genome Research Institute (NHGRI)
National Institutes of Health
Department of Health and Human Services
Genetic Discrimination
https://www.genome.gov/about-genomics/policy-issues/Genetic-Discrimination

Genetic Information Nondiscrimination Act Guidance (2009)
Office for Human Research Protections
Department of Health and Human Services
https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-genetic-information-nondiscrimination-act/index.html

Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable
U.S. Food and Drug Administration
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-informed-consent-in-vitro-diagnostic-device-studies-using-leftover-human-specimens-are-not

Coded Private Information or Specimens Use in Research, Guidance (2008)
Office for Human Research Protections
Department of Health and Human Services
https://www.hhs.gov/ohrp/regulations-and-policy/guidance/research-involving-coded-private-information/index.html
OHRP Guidance
Office for Human Research Protections
Department of Health and Human Services
https://www.hhs.gov/ohrp/regulations-and-policy/guidance/index.html

Informed Consent Policy Guidance

Office for Human Research Protections
Department of Health and Human Services
https://www.hhs.gov/ohrp/index.html

Issues to Consider in the Research Use of Stored Data or Tissues (1996, 1997)
Office for Human Research Protections
Department of Health and Human Services

https://www.hhs.gov/ohrp/regulations-and-policy/guidance/issues-to-consider-in-use-of-stored-data-or-tissues/index.html

Regulations, Policy & Guidance
Office for Human Research Protections
Department of Health and Human Services
https://www.hhs.gov/ohrp/regulations-and-policy/index.html#informed

Withdrawal of Subjects from Research Guidance (2010)
Office for Human Research Protections
Department of Health and Human Services
https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-withdrawal-of-subject/index.html

Informatics System Security

Risk Management Guide for Information Technology Systems
National Institute of Standards and Technology
https://www.archives.gov/files/era/recompete/sp800-30.pdf

Security and Privacy Controls for Information Systems and Organizations, NIST SP 800-53 Rev. 5
National Institute of Standards and Technology
https://csrc.nist.gov/pubs/sp/800/53/r5/upd1/final

Laboratory Practices

Clinical Laboratory Improvement Amendments
U.S. Centers for Disease Control and Prevention
http://www.cdc.gov/clia/

Good Laboratory Practices
Organisation for Economic Co-operation and Development (OECD)
https://www.oecd.org/en/publications/good-laboratory-practice_9789264012837-en.html

International Organization for Standardization (ISO9000)
http://www.iso.org/iso/home.htm

International Society for Biological and Environmental Repositories (ISBER)
http://www.isber.org

Quality Systeme Regulation
Code of Federal Regulations
https://www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-820

National Cancer Institute

National Cancer Institute
National Institutes of Health
https://www.cancer.gov/

Biorepositories and Biospecimen Research Branch
National Cancer Institute
National Institutes of Health
https://dctd.cancer.gov/programs/cdp/organization/bbrb

Biospecimen Research Database
Biorepositories and Biospecimen Research Branch
National Cancer Institute
National Institutes of Health
https://brd.nci.nih.gov/brd/

Biobank Economic Modeling Tool
National Cancer Institute
National Institutes of Health
Code available at: https://github.com/NCIP/BEMT

NCI Specimen Resource Locator
National Cancer Institute
National Institutes of Health
https://specimens.cancer.gov/

Symposium-Workshop on Custodianship and Ownership Issues in Biospecimen Research
National Cancer Institute
National Institutes of Health
https://dctd.cancer.gov/data-tools-biospecimens/biospecimens-biobanks/resources/bbrb-workshop-summaries-reports

NIH Policies and Guidelines

Certificates of Confidentiality (CoC)
Grants & Funding
National Institutes of Health
https://grants.nih.gov/policy-and-compliance/policy-topics/human-subjects/coc

Financial Conflict of Interest
Grants & Funding
National Institutes of Health
https://grants.nih.gov/policy-and-compliance/policy-topics/fcoi

Research Involving Recombinant or Synthetic DNA Molecules
NIH Grants Policy Statement
National Institutes of Health
https://grants.nih.gov/grants/policy/nihgps/html5/section_4/4.1.26_research_involving_recombinant_or_synthetic_nucleic_acid_molecules__including_human_gene_transfer_research_.htm

NIH Scientific Data Sharing
National Institutes of Health
https://grants.nih.gov/policy-and-compliance/policy-topics/sharing-policies

NIH Genomic Data Sharing Policy
National Institutes of Health
https://grants.nih.gov/policy-and-compliance/policy-topics/sharing-policies/gds

Sharing Research Resources
NIH Grants Policy Statement 8.2.3
National Institutes of Health
https://grants.nih.gov/grants/policy/nihgps/html5/section_8/8.2.3_sharing_research_resources.htm

Other Biospecimen Resource References

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

Handbook of Human Tissue Sources–A National Resource of Human Tissue Samples
RAND
https://www.rand.org/pubs/monograph_reports/MR954.html

Standardized Systems for Clinical and Pathology Data

American Joint Committee on Cancer: Cancer Staging Systems
https://www.facs.org/quality-programs/cancer-programs/american-joint-committee-on-cancer/cancer-staging-systems/

Program in Evidence-Based Care
Cancer Care Ontario
https://www.cancercareontario.ca/en/cancer-care-ontario/programs/data-research/evidence-based-care

Cancer Protocols
College of American Pathologists
https://www.cap.org/protocols-and-guidelines/cancer

International Classification of Diseases (ICD)
World Health Organization (WHO)
https://www.who.int/classifications/classification-of-diseases

International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3)
World Health Organization (WHO)
https://www.who.int/standards/classifications/other-classifications/international-classification-of-diseases-for-oncology

National Comprehensive Cancer Network (NCCN) Guidelines
NCCN
https://www.nccn.org/guidelines/category_1

Data Standards and Data Dictionary
North American Association of Central Cancer Registries
https://www.naaccr.org/data-standards-data-dictionary-version-archive/

Systematized Nomenclature of Medicine—Clinical Terms® (SNOMED CT)
SNOMED International
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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.[7] 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, Fifth Edition* (2023), and RAND Corporation's *Case Studies of Existing Human Tissue Repositories* (2003); or relevant Websites such as the CDC Website. 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 (CDC, Special Pathogens Branch, Glossary of Terms, http://hickmanchartersciolv.pbworks.com/f/Glossary,_,CDC,Special,Pathogens,Branch.pdf .

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

Aliquot. 1. Pertaining to a portion of the whole; any one of two or more samples of something, of the same volume or weight (NCI Thesaurus). 2. Subdivided portions of a specimen that are stored individually. Note that aliquots may not always be homogenous, *e.g.*, tissue specimen aliquots such as sections or slides. (ISBER 2023).

Analyte. Component represented in the name of a measurable quantity. This includes any element, ion, compound, substance, factor, infectious agent, cell, organelle, activity, property, or other characteristics which are to be determined. (ISBER 2023).

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

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

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

[7] 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/.

Audit. 1. A review and/or practical observation of procedures, records, personnel functions, equipment materials, facilities, and/or vendors performed internally (e.g., by parent organization) or by a third party that is documented in order to evaluate adherence to documented standard operating procedures (SOPs) or applicable by laws and regulations. (ISBER 2023). 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 Dictionary of Cancer Terms).

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).

BSL. Specific combinations of work practices, safety equipment, and facilities, which are designed to minimize the exposure of workers and the environment to infectious agents. BSL-1 applies to agents that do not ordinarily cause human disease. BSL-2 is appropriate for agents that can cause human disease, but whose potential for transmission is limited. BSL- 3 applies to agents that may be transmitted by the respiratory route which can cause serious infection. BSL- 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 (CDC Special Pathogens Branch, Glossary of Terms).

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 (OSHA Bloodborne Pathogen Standards, 29 CFR § 1910.1030).

Certificate of Confidentiality. Issued by the 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 (NIH Certificates of Confidentiality Website).

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

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

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

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

Common data elements. A data element that is common to multiple data sets across different studies, surveys, or registries. The intentional use of CDEs improves data quality and promotes data sharing (NIH Toolkit for Patient-Focused Therapy Development: 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: http://www.gpo.gov/fdsys/pkg/CFR-2013-title42-vol1/pdf/CFR-2013-title42-vol1-sec50-605.pdf). 2. Prejudice or bias that may occur when one's impartiality is compromised by opportunities for personal gain or occupational advancement, or by the chance that one's work may support a favored point of view or social agenda (Taber's Medical Dictionary).

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

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

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

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

Database of Genotypes and Phenotypes. The National Institutes of Health (NIH) sponsored repository charged to archive, curate and distribute information produced by studies investigating the interaction of genotype and phenotype (NCI GDC Documentation).

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 2023).

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).

Disposition. Process of permanently and wholly eliminating a specimen, collection, or stored data beyond repair or re-instatement. May also be referred to as destruction or culling (ISBER 2023).

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. An individual who receives and uses specimens and/or data or partakes in services offered by the repository (ISBER 2023). 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 NIH (*NCI Best Practices* working definition).

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

Globally Unique Identifier. A 128 bit identifier. Depending on the mechanism used to generate it, it is either guaranteed to be different from all other unique universal identifiers/globally unique identifiers generated until 3400 AD or extremely likely to be different. Its relatively small size lends itself well to sorting, ordering, and hashing of all sorts, storing in databases, simple allocation, and ease of programming in general (NCI Thesaurus).

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

Human research participant. See Human subject.

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

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

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

Informed consent. A decision to participate in research, taken by a competent individual who has received the necessary information; who has adequately understood the information; and who, after

considering the information, has arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation (Council for International Organizations of Medical Sciences [CIOMS]. International Ethical Guidelines for Biomedical Research Involving Human Subjects. "Guideline 4: Individual Informed Consent" [2002]).

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

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

Intellectual property (IP). 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. Ability of two or more systems or components to exchange information and to use the information that has been exchanged (NCI Thesaurus).

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).

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 2023).

Longitudinal data. Data that track the same sample at different points in time (U.S. Department of Labor, National Longitudinal Surveys, What are Longitudinal Data?, https://nlsinfo.org/content/getting-started/what-are-longitudinal-data).

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 2023).

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).

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 2023).

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 2018).

Process validation studies. The process of demonstrating that a specific procedure will consistently produce expected results within predetermined specifications (ISBER 2018).

Processing. Any procedure employed after biospecimen collection but prior to its distribution, including preparation, testing, and releasing the biospecimen to inventory and labeling (ISBER 2023).

Project management. The application of knowledge, skills, tools and techniques to a broad range of activities to meet the requirements of the particular project.

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

Quality. Conformance of a biospecimen or process with pre-established specifications or standards (ISBER 2018).

Quality assurance. A broad approach for aiming to prevent issues within processes that could impact on the fitness for purpose of specimens and data. Part of quality management (ISBER 2023).

Quality control. A standardized process of proactively defining quality requirements, monitoring selected indicators based on these requirements, and identifying and responding to quality issues to support fitness for purpose of specimens, associated data, or services. Part of quality management and complementary to quality assurance (ISBER 2023).

Quality management system. Integrates policies and practices for the full spectrum of quality in a repository. Can be facilitated manually, e.g., with paper-based documentation, supplemented by electronic systems, or be entirely based on a software solution, according to the resources available to the repository (ISBER 2023).

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. Accessing specimens or data for use, transfer, processing, distribution, and/or disposal (ISBER 2023).

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 MTA approved for use at the NIH. The NIH encourages the use of the SLA to facilitate exchanges between academic institutions (NCI Technology Transfer Branch, https://www.techtransfer.nih.gov/sites/default/files/documents/policy/pdfs/503-a-policy.pdf).

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

Specimen. See Biospecimen.

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

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

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

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

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

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

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

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

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

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

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

ACRONYM LIST

API	Application Programming Interface
BAP	CAP Biorepository Accreditation Program
BEBP	Biospecimen Evidence-Based Practices
BBRB	NCI Biorepositories and Biospecimen Research Branch
BLOODPAC	Blood Profiling Atlas in Cancer
BMBL	Biosafety in Microbiological and Biomedical Laboratories
BPV	NCI BBRB Biospecimen Pre-analytical Variables Program
BRD	Biospecimen Research Database
BRN	NCI BBRB Biospecimen Research Network
BSL	biosafety level
CAP	College of American Pathologists
CDC	Centers for Disease Control and Prevention
CDE	Common Data Element
CEN/TS	European Committee for Standardization
cfDNA	cell-free DNA
CFR	Code of Federal Regulations
CMS	Center for Medicaid and Medicare Services
COI	conflict of interest
CRDC	Cancer Research Data Commons
CSF	cerebrospinal fluid
dbGaP	database of Genotypes and Phenotypes
DHHS	U.S. Department of Health and Human Services
DNA	deoxyribonucleic acid
EFLM	European Federation of Clinical Chemistry and Laboratory Medicine
FDA	U.S. Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
GDPR	European General Data Protection Regulation

GDS	NIH Genome Data Sharing
GINA	Genetic Information Nondiscrimination Act
GUID	Global Unique Identifier
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
ISBER	International Society for Biological and Environmental Repositories
ISO	International Organization for Standardization
LIMS	Laboratory Information Management System
LN2	Liquid nitrogen
miRNA	microRNA
mRNA	messenger RNA
MTA	material transfer agreement
NCI	National Cancer Institute
NHGRI	National Human Genome Research Institute
NIST	National Institute of Standards and Technology
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OSHA	Occupational Safety and Health Administration
PCR	polymerase chain reaction
PHI	protected health information
PHS	Public Health Service
PII	personally identifiable information
QA/QC	quality assurance/quality control
QMS	quality management system

RNA	ribonucleic acid
SOP	standard operating procedure
SPIDIA	Standardisation and improvement of generic Pre-analytical tools and procedures for In-vitro DIAgnostics project
SPIDIA4P	SPIDIA for Personalized medicine
TCGA	The Cancer Genome Atlas
TCIA	The Cancer Imaging Archive

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