BEST PRACTICES:
Recommendations for Repositories
Fourth Edition

isber

INTERNATIONAL SOCIETY FOR BIOLOGICAL AND ENVIRONMENTAL REPOSITORIES

These Best Practices are reviewed periodically and revised to incorporate improved application and research findings that would affect repository work. The reader is advised to check the ISBER web site (www.isber.org) to ensure that the most recent version is available for use.

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INTRODUCTION

ISBER BEST PRACTICES: RECOMMENDATIONS FOR REPOSITORIES

The availability of high-quality biological and environmental specimens for research purposes requires the development of standardized methods for collection, handling, storage, retrieval, and distribution. The International Society for Biological and Environmental Repositories (ISBER) is the leading global forum for the development, management, and operations of repositories. One of the key objectives for ISBER is to share successful strategies, policies, and procedures on providing fit-for-purpose specimens for research. For more information about ISBER see www.isber.org.

ISBER Best Practices: **Recommendations for Repositories (Best Practices) is a guidance document that reflects the collective experience of its members and has received broad input from other repository professionals.**

Throughout this document, effective practices are presented for the management of specimen collections and repositories and the term "Best Practice" is used in cases where a level of operation is indicated that is above the basic recommended practice or more specifically designates the most effective practice. It is understood that physical location or financial constraints can make "Best Practices" difficult or impossible to attain. Repositories facing such challenges should decide how best to incorporate these recommendations. While adherence to ***ISBER Best Practices*** is voluntary, it is important to note that some aspects of specimen management are governed by national/federal, regional, and local regulations. The reader should refer directly to their own national/federal, regional, and local regulations and requirements, as appropriate.

ISBER recognizes that the definition and subsequent use of the terms "specimen" and "sample" varies when used in a clinical versus biodiversity and/or environmental setting. Definitions for each context are provided in the glossary. While "specimen" is used predominantly throughout the document, it could be substituted for "specimens and/or samples" in most instances.

ISBER has strived to include terminology associated with various specimen types covered under these practices, but here too, readers should take steps to ensure that recommendations are appropriate for their particular repository type. Important terms within the document are italicized when first used in a section and defined in the glossary.

The ***ISBER Best Practices*** are periodically reviewed and revised to reflect advances in research and technology. The fourth edition builds on the foundation established in previous editions which were published in 2005, 2008, and 2012.

SECTION A: REPOSITORY PLANNING CONSIDERATIONS

A1. GENERAL

A *repository* is defined as a formally managed physical or virtual entity that may receive, process, store, and/or distribute *specimens* and/or *samples* and their associated data as appropriate in support of current or future use. A repository may be further defined by the collection of specimens as a *biorepository* if the specimens represent, or are biological specimens. Specimens may be collected for a variety of scientific purposes (*e.g.*, basic, clinical, population, public health, environmental, agricultural, museum-based research). The specimens may be stored whole, processed and *aliquoted*, derived, or be stored as reference specimens from a study population (*e.g.*, type specimen).

A repository may be physically or virtually developed for a single organization or its services may be contracted or outsourced to serve other organizations. All repositories should be planned, organized, and managed in accordance with applicable ethical and legal frameworks and comply with national/federal, regional, and local regulations.

Many issues briefly touched upon in this section have been explored more fully in subsequent sections of these Best Practices. The reader should refer to the Table of Contents to identify sections appropriate to their particular interests and needs.

A2. REPOSITORY GOVERNANCE

Repository governance is the implementation and oversight of policies and procedures that regulate operations. Governance structure, design, and complexity may vary greatly by repository size, purpose, source of support, and institutional affiliation. Governance structure should comply with applicable regulations, provide good stewardship of repository specimen and data collections to include *quality control* through Quality Management System adherence (see Section D: Quality Management), and be part of a business plan that addresses long-term sustainability (see Section A3.1. Organizational Planning Considerations). Governance oversight may be provided by a committee, board, or other group (governance oversight body) that serves to guide and advise the repository. A governance framework and/or policy should be developed to include a description of the governance oversight body's composition and responsibilities.

Governance policies and procedures should be developed with the full *repository lifecycle* in mind (see Section M Specimen Access, Utilization, and Disposition). It is important that repository leadership, specimen, and data access review committees and repository operation policies be available to stakeholders.

Transparency is the basis of repository stakeholder trust, including but not limited to that of *donors*, scientists, sponsors, and the general public. Information regarding the ethical, legal, and social foundations of the repository's activities, repository governance, services provided, and fees assessed, if any, should be made available to stakeholders. Consideration may be given to providing this information electronically through a publicly accessible website, which may also serve to inform the scientific community of the repository's activities.

Best Practice: A repository should have a governing body and written policies covering the full repository lifecycle.

Best Practice: Repository business plans should include terms and conditions of the repository governance oversight body.

Best Practice: Information regarding the repository's operational and governance structures should be made available to stakeholders.

A2.1. Elements of a Repository Governance Plan

A written repository specimen and data governance plan should be made available to stakeholders and should be incorporated in the repository business plan (see Section A3.1. Organizational Planning Considerations). Elements of a repository governance plan should include:

- Provisions for safekeeping of the collection(s) including maintenance, security, and integrity of specimens and data (see Section B: Facilities).
- A transparent policy regarding specimen and data access and use including applicable requirements, limits, exclusions, and priorities (see Section M: Specimen Access, Utilization, and Disposition).
- Communication tools making general repository operations and policies available to stakeholders (see Section A3.4. Communication).
- A plan for appropriate physical and electronic management of specimens and data in the event of a collection's utility end, resource constraints,

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lapses in funding, donor withdrawal, dissolution of the repository, or disaster recovery (see Section M: Specimen Access, Utilization, and Disposition).

Best Practice: A widely distributed, readily available, written specimen and data governance plan should be incorporated in the repository business plan.

A3. REPOSITORY DEVELOPMENT

A3.1. Organizational Planning Considerations

A business plan is essential to the development of a repository. Business planning for the development of a repository should include identifying target customer(s) or business stakeholder needs, identifying the infrastructures (*e.g.*, staffing, facilities, equipment) and services to serve the identified customer(s) and business needs, establishing proactive review of the repository's ability to meet the needs, and a robust marketing plan to advertise the facilities and services within and outside the organization. The business plan should include a governance framework with transparent access guidelines and processes to support utilization of the repository collection(s). Considerations for termination of specific collections and/or the repository should also be included, as applicable.

When planning a repository, it is important that the vision and mission be clearly defined. The vision defines the direction of the repository. The mission should address the purpose of the repository and the entities served by the collections obtained. The vision and mission should be reviewed over time to ensure its appropriateness as conditions surrounding its implementation may change. It is also important that the governance, equipment, facilities, staffing, and funding for a repository be established according to a structure that will support its mission and activities during its anticipated lifetime. Policies should be created, enforced, and reviewed on a regular basis concerning repository operations from initiation to termination.

Best Practice: A business plan should be developed for the lifetime of the repository and should be updated on a regular basis (*e.g.*, every 2 years) or as requested.

A3.2. Determination of Specimens to be Collected and Storage Environment

The type of specimen that is best suited for a particular scientific investigation will depend on the goals of the particular research effort supported. Some material types are better suited than others for some kinds of analyses over others. Material type and quantity, specimen source, downstream testing plans, and financial constraints may influence decisions regarding specimen collection. Repositories should determine the most appropriate storage environment for the particular types of specimens it holds together with their intended use and ensure that the sufficient equipment, facilities, and funding are in place to support the storage of these specimens until they are needed.

Policies should be established for the acquisition of new specimens and for *culling* or deaccessioning of collections when specimens have fulfilled their original purpose, are no longer suitable for their intended purpose, or if participants request the withdrawal of their specimens (see Section M3. Specimen or Collection Disposition).

Best Practice: The scientific purpose of the specimen collection should be defined prior to initiation to effectively plan for collection, processing, storage, and downstream uses. The plan should include exclusion criteria, if any, for specimens that prove difficult to collect.

A3.3. Determination of Customers Served

Repositories should develop a clear understanding as to the identity and needs of the investigators and scientific clients it serves. Whenever possible, efforts should be made to understand the downstream use planned to ensure that specimens provided are collected and processed in a manner that is likely to benefit future research efforts.

Best Practice: Repositories should create a plan to receive feedback from users to make sure that customers' needs have been satisfied to the greatest extent possible. This is one component of a total Quality Management System.

A3.4. Communication

Transparent and effective lines of communication should be established among stakeholders, including research participants, and should be part of a *Standard Operating Procedure* (SOP). Trust is an essential component among those donating, *processing*, and storing specimens, as well as among the investigators who use the specimens to pursue a scientific endeavor. Efforts should be made to ensure that trust is developed and maintained and could include the engagement of advocates as part of the stakeholder community.

Best Practice: Prior to the initiation of collection efforts, stakeholders should gather to talk about communication strategies to ensure that expectations are satisfied and that transparency and trust can be firmly established.

Best Practice: Repositories should develop clear guidance as to what services are provided, the costs for the provision of those services, the hours during which services are available, and contact information appropriate for each category of stakeholder for regular hours as well as for after-hour emergencies.

A3.5. Establishing Repository Models

The collection and storage of specimens of various types (*e.g.*, human, animal, plant, environmental, bacterial) may be performed in support of a variety of scientific endeavors. Specimens may be collected as a part of *prospective* or *retrospective* studies and the methods of collection, processing, and *distribution* of these specimens may depend on resource constraints, legal constraints, and the particular scientific inquiry under consideration. Several models exist for how specimens may be procured, stored, and prepared for subsequent use that may be impacted by such constraints. A repository may take advantage of a single approach or multiple approaches to achieve its mission. Once a repository is established in support of a model, it may be possible to join with additional models, as appropriate. This approach prevents duplication of effort and allows more efficient utilization of resources. Regardless of the model employed, specimens should always be collected and processed according to the most current methods supported by scientific data and best practices, where possible.

A3.5.1. Investigator-driven and Institutional Collections

The collection of specimens and utilization of a repository can be driven by a single investigator or group within an institution. These specimens may be available through collaboration or for general use. Repositories that store specimen collections obtained for defined study purposes may serve a single facility or provide centralized storage and processing for a large number of studies as part of a centralized repository service, acting as the *custodian* of the collection(s). Decisions about which specimens and data are collected are typically made by an individual investigator or team of investigators and are defined by study goals. Specimens are obtained and processed by trained field staff, clinical sites, or hospitals according to SOPs (see Section D: Quality Management). These repositories may be operated by institutional staff or through contracted repository services.

A3.5.2. Federated Collections

Federated collections (*e.g.*, networks) are created when specimens are collected, processed, and stored at physically separated sites, while related data are managed or duplicated through a central *database*. Each site functions as the specimen custodian for its local collection. Specimens are requested through the central database and distributed by the site custodians. Federated network participation may require that a portion of each custodian's collection be made available to other network participants. This federated model may increase utilization of network collections.

A3.5.3. Virtual Collections

Virtual collections are virtual representations of specimens (*e.g.*, digital pathology images, hematoxylin and eosin (H&E) stained slides, slides of tissue prepared for immunohistochemical analysis, digital images of specimens, molecular data) that are housed and analyzed elsewhere or represent catalogs of specimens stored elsewhere. Virtual representations allow for new scientific questions to be addressed using specimens that have already been processed (*e.g.*, slides containing tissues prepared for immunohistochemical analysis, digital images of

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specimens, molecular data). Publicly-available data from Genome-Wide Association Studies would be included in this category.

Catalogs of physical specimens and associated data allow investigators to access these previously collected resources. Various formats exist, including those that *document* single organization resources, multiple organization resources, or even multiple catalogs. Utilization of human specimens may be based on the related research protocol and consent provided by donors. Information about available specimens is often provided in the form of a searchable electronic inventory that can be used to identify the desired specimens. The catalog may provide contact information for a requestor to communicate directly with the collection custodian to learn of access policies required for the actual sharing of specimens and associated data. Catalogs allow investigators to identify resources that are currently available rather than having to initiate new and sustained collection efforts that can be time-consuming and costly.

A3.5.4. Biodiversity and Environmental Biobanks

Biodiversity biobanks and *environmental specimen banks* (ESBs) are often attached to *natural history collections*, universities, or environmental or agricultural organizations. Specimens and data may have been collected by individual scientists specifically for their own research, through surveys, or as part of generic collecting expeditions, and may pass through a registrar's office. The collections usually provide material to the wider scientific community, safe-guard biodiversity, and document environmental change. Depending on size, organisms may be stored whole or as a portion (*e.g.*, tissue, blood, leaf sections) of the original specimen.

A3.6. Determination of Services to be Provided

Repositories should determine the services to be provided and put into place the appropriate infrastructure necessary to ensure that high-quality specimens will be available for future research. The infrastructure not only includes equipment and supplies but also the trained personnel to perform these services as needed. Services may include specimen collection, receipt into the repository, processing, quality control, storage, and distribution. Multiple processing pathways may need to be developed within the repository to meet business needs and investigators' requirements.

There are a number of services that a repository may provide in addition to the collection and storage of specimens. Examples of these include feasibility assessments to assist investigators with study planning and proposal submissions, the provision of letters of support or the establishment of collaborative relationships with investigators, the identification and/or consenting of participants, batching of specimens, and inclusion of quality control specimens for specimens destined to be sent to a laboratory for testing, histology services, micro-dissection, nucleic acids extraction and analysis, etc. All services offered should be well-defined. Consideration should be given to fees-for-service where appropriate, to support sustainability. Fee schedules should be established and posted prior to provision of service, when applicable. Consistency and transparency should exist in the application of service fees (see Section A4. Funding and Other Financial Considerations).

A3.6.1. Procurement Service

A repository that provides procurement services, or request-based services, collects and processes specimens for specific requests on an ''as-needed'' basis. Investigators state what specimens they are seeking and frequently supply the protocol for collection, handling, and storage. The repository attempts to collect specimens specifically for that request and processes them according to the investigator's specifications. The service provider should be prepared to share guidance per evidence-based collection practices for the material type being requested. A repository based on this model will most likely not require long-term storage if the specimens will be entirely transferred to requestors within a short time after collection. The service provider should have a way to track specimen inventory and data moving into and out of the repository. Initial data collected with the specimens should be transferred to the requestor according to the protocols under which the data and specimens were collected and will be received, but this

model does not facilitate long-term follow-up data associated with the collections.

A3.6.2 Banking Service

Banking involves the storage of specimens in anticipation of current and future needs. Investigators seeking a particular type of specimen can approach a repository that has banked specimens to see if the desired specimens are available among the existing collections. Banked specimens may be received into the repository from a variety of sources including, but not limited to, agreements with clinical sites, hospitals, institutions, or for biodiversity and environmental banks from staff or researchers who collect specimens during their field work. Specimens are subjected to identical processing procedures using pre-defined protocols to ensure standardized practices. Data associated with banked specimens may be limited to what is available at the time of collection.

One particular type of bank, a disease-focused bank, may be initiated by advocacy groups, to advance for research a particular disease or syndrome. Donors and families may request that hospitals and other clinical sites send their specimens to these banks or specimens may be donated through specimen collection kits sent from the donor's residence (termed a donor's ''self-collected'' specimen). Advocacy-oriented banks often have associated registries containing detailed clinical and follow-up information. These resources can be a rich source of material and data for research. Specimens and information from family members may also be associated with these banks.

A4. FUNDING AND OTHER FINANCIAL CONSIDERATIONS

The cost for specimen collection, processing, storage, quality control, and distribution can be considerable and it is important for repositories to develop a financial plan for the expected lifetime of the specimen storage and handling activities. Plans should be reviewed on a regular basis and adjusted as needed. See Section H: Cost Management for a full review of financial considerations when starting and implementing a repository.

A5. REPOSITORY PERSONNEL

Repository staff varies according to the needs of the organization and the services provided and may be composed of managerial staff, technical staff, administrative personnel, and/or support staff. Personnel should be adequately trained to perform the tasks required by their particular position description and should follow all repository policies and applicable national/federal, regional, and local regulations.

Best Practice: An organizational structure and clear job descriptions with lines of reporting should be documented for each role in the repository.

A5.1. Director

The individual(s) responsible for oversight of repository management (*i.e.*, Director, Head, Curator, Manager) is referred to in this *document* as the Director. The Director should be qualified by training and experience to direct and manage the scope of activities conducted by the repository.

A5.1.1. General Operations

The Director should implement policies of the organization and should be responsible for all operations including compliance with current international, national/federal, regional, and local regulations. Depending upon organizational structure of the repository, the Director may have other responsibilities including:

- Ensuring the repository operates within budget.
- Ensuring the repository has adequate funding for operations which may require the development of cost-recovery strategies to ensure the repository's short and long-term financial stability.
- Ensuring that an adequate policy is in place for access to the specimens stored in the repository and that requests for specimens are met in a timely fashion.
- Serving as a liaison to key stakeholders.
- Ensuring that activities are within national/federal, regional, local, and international ethical, legal, and social norms, as applicable.

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- Ensuring confidentiality of data.
- Ensuring that SOPs and best practices are in place and in general use as part of a Quality Management System.

A5.1.2. Personnel Supervision

The Director should construct and maintain an organizational chart that delineates the functional relationships within the repository. Candidates for the supervisory and technical staff should be approved by the Director. The Director should also approve and maintain job descriptions and document staff responsibilities. The Director should ensure that personnel responsible for performing repository activities are adequate in number and experience and have assigned responsibilities commensurate with their capabilities.

The Director should also be responsible for developing and reviewing employee training programs. They should ensure that the repository is in alignment with applicable ethical and legal frameworks and is compliant with national/federal, regional, and local regulations.

A5.1.3. Quality Management System

The Director and/or the Quality Manager should ensure that a *Quality Management System* (QMS) is in place to ensure that operations follow the repository's manual of operations and SOPs and comply with applicable requirements of governmental and regulatory organizations. The Director should require regular, documented, internal reviews or audits to ensure compliance with SOPs and regulations and to satisfy *end-user* requirements (see Section D: Quality Management). If *deviations* from SOPs or quality indicators are identified, the Director should ensure that appropriate corrective action is undertaken successfully and documented (see Section D4.3.3. Non-conformities).

A5.2. Technical Staff

The scope of activities carried out by the repository technical staff may include, but not be limited to, specimen collection, processing, quality control, shipping and receiving, storage, data management, or facility and equipment management. Managers and staff should possess sufficient educational background, experience, and training to ensure that assigned tasks are performed in accordance with the repository's established SOPs. Technical staff should be responsible for adherence to policies and SOPs as established by the Director. Duties of each staff member should coincide with written job descriptions. Staff should demonstrate competency in operations for which they have received training and to which they are assigned. Authority and reporting relationships for each member of the staff should be clearly described.

Best Practice: An organizational structure and clear job descriptions with lines of reporting should be documented for each role in the repository.

A6. CONTRACTED LABORATORY SERVICES AND CONSULTANTS

Careful planning during the development phase is critical to quality and cost-efficiency. Where internal resources are not sufficient to provide all necessary expertise, either during development or as a repository evolves, a repository may seek assistance from qualified experts and consultants. Consultants should have documented successful experience (similar to that which would be sought for internal staff) in the area for which they are retained. Repository consultants may provide expertise in areas such as strategic planning; equipment selection; and decisions surrounding automation, SOP development, vendor selection, grants and cost recovery, contract management, quality assurance, and regulatory affairs. Similarly, the repository may have contractual relationships with other institutions or service providers that provide access to facilities or services not available at its own location or through other departments within a parent institution (when applicable). In all of these situations, the Director should have clear documentation of the relationships, rights, and obligations of all parties.

Best Practice: Repositories that contract for services should retain records pertaining to the name and address of the contracted facility, the name and contact information for key personnel at the location where the services are being provided, documentation of the inclusive dates of the contract or agreement period, and copies of the contract as well as any accompanying documentation. The scope of work for all contract services should be clearly articulated.

Best Practice: Repositories should perform supplier evaluation when contracted services are required.

SECTION B: FACILITIES

B1. GENERAL

An efficient *repository* has many particular location and design elements to ensure the safe-keeping of the material stored, support the equipment employed, and provide a safe and effective working environment for the repository staff. In planning the design of a repository, it is necessary to know the types of material being stored, the required storage and handling conditions, the projected retention periods, projected growth of the *specimen* numbers, and the projected use of the materials. The design should include sufficient space to accommodate the material planned for initial, future, and backup storage and also provide for the safe movement of people, equipment, and specimens, as needed, or as required by law and/or other regulatory agencies.

Best Practice: Planning for a repository within a facility should take into account the environmental conditions experienced by the region where it is located (*e.g.*, fire, flooding, high winds, earthquake, tsunami) and availability of resources (*e.g.*, access to chilled water, stable electricity, liquid nitrogen). A disaster recovery plan should be established for the repository per Section B8. Emergency Preparedness.

B2. HEATING, VENTILATION, AND AIR CONDITIONING

B2.1. Temperature

In most repositories it is critical to maintain ambient temperature within defined limits. Sufficient heating capacity should be provided to prevent the freezing of water in drain lines. Likewise, sufficient air conditioning should be provided to prevent excess load on the compressor systems of mechanical freezers and refrigerators that may result in excess wear and early failure.

Best Practice: For optimal life of mechanical refrigeration equipment, repository ambient temperatures should be monitored and controlled following the manufacturers' instructions for temperature and humidity. This is particularly critical for rooms containing multiple mechanical units.

B2.2. Air Flow, Circulation, and Humidity

Sufficient air circulation should be provided to prevent excess moisture and condensation. Excess humidity can lead to fungal growth if left unchecked, which may affect specimen integrity and cause health problems for staff. Sufficient space for air circulation is required especially in areas where freezers and refrigerators are employed to prevent excess heat accumulation which may negatively affect compressor function (see Section C3. Mechanical Freezers). Adequate ventilation and monitoring are also critical in repositories where liquid nitrogen and *dry ice* are used to ensure that sufficient oxygen levels are maintained (see Section C2.5.1 Oxygen Sensors). Similarly, when services are performed in which potentially harmful vapors are generated (*e.g.,* formaldehyde) the ventilation system should ensure that personnel are protected and that national/federal, regional, and local regulations for the removal of specific harmful vapors are met.

Best Practice: Appropriate monitoring devices (*e.g.,* oxygen and/or CO_2 monitors), preferably with auditory and visual alarms, should be combined with a dedicated exhaust system and installed within areas where low oxygen level might develop or harmful gases might accumulate. This system provides a sufficient amount of recirculating air to replace the air volume of a room according to the local regulations. The extracted gases are vented to the outside of the building, according to regulations, and never to the interior areas of the building.

Best Practice: Repositories located in areas where humidity is high (*e.g.*, coast) should employ a de-humidification system to ensure optimal operation of the equipment.

B3. LIGHTING

B3.1. General Lighting

Lighting in a repository should be sufficient to provide a safe working environment and to allow materials to be accurately stored and retrieved. The lighting levels required will depend on the particular spatial environment where the *samples* are stored, the type of activity that is being performed, the volume and specimen type, and the labeling/identification system employed.

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Lighting may be both general and task-focused, depending on the situation. Some repositories may contain materials or specimens which are sensitive to light levels or to particular frequencies of light.

Best Practice: Appropriate lighting should be planned for and used during the storage and handling of materials or specimens determined to be sensitive to certain lighting conditions.

B3.2. Task Lighting

Task lighting may be necessary to have sufficient illumination for tightly packed materials, reading *labels*, or where overhead lighting is impaired. In situations where task lighting is employed, care should be taken that the lighting method does not adversely affect the sample integrity and the storage conditions. For example, the heat from incandescent lighting placed too close to stored material may cause a sample to thaw, partially thaw, or melt. Consider using Light Emitting Diodes (LEDs), given this type of lighting is more energy efficient, cost effective, and easier to produce directed beams of light for work stations.

Best Practice: LED lighting or another type of lighting that does not create a source of heat should be used in task lighting near work areas used to handle specimens.

B3.3. Emergency Lighting

In case of power loss, it is critical that emergency lighting be available to indicate exit routes from the repository and to provide an illuminated, safe environment to aid in monitoring equipment and responding to the needs of the emergency. Emergency lighting should have battery backup support and should be tied to backup generators. It may be beneficial to use small night lights that plug into outlets that have a battery component for low-level illumination. Repositories should also have portable lighting (*e.g.,* flashlights) on hand to use as focused light sources, as needed. Focused light sources can be essential during an emergency for use in equipment diagnosis and repair.

Best Practice: Emergency lighting should be tested on a regular basis and batteries checked on an annual basis and replaced as needed as a part of the overall operating procedures.

B4. FLOORING

Flooring surfaces used in repositories should be appropriate for the equipment and refrigerants used in daily repository activities. Flooring should be easy to clean and facilitate the movement of equipment when circumstances warrant. Special consideration should be given to the flooring in regions where *liquid nitrogen* is used, as vinyl tile will crack and cause a hazard if liquid nitrogen is spilled directly onto it. Repositories should consider providing anti-fatigue mats for staff in areas where personnel stand for prolonged periods of time.

Due to the high weight of storage and other equipment (*e.g.*, freezers, liquid nitrogen units, heavy cabinets), consideration of the combined weight of the equipment must be taken into account when locating the repository within a building or when designing a new facility.

B5. BACKUP POWER

Repositories that store specimens in constant temperature environments will use some equipment that require a source of constant and stable (*e.g.*, consistent voltage per manufacturers' instructions) electrical power. Given that all commercial power is likely to be interrupted at some time, a backup power system is strongly recommended.

Best Practice: Repositories should be aware of the location of their building generators and confirm that they are on the backup system.

B5.1. Uninterruptible Power Supply

An uninterruptible power supply (UPS) is inserted between the source of power (typically commercial utility power) and the load it is protecting. When a power failure or abnormality occurs, the UPS will effectively switch from utility power to its own power source almost instantaneously to provide a continuous supply of electric power during transition to an alternate power source or orderly shut-down.

Best Practice: Computer systems and electronic systems such as *environmental monitoring systems*, safety systems (*e.g.*, oxygen sensors, ventilations systems), and controllers for liquid nitrogen freezers should be protected by a UPS. UPSs used in repositories should be tested on an annual basis to ensure their proper backup capabilities.

B5.2. Generators

The most common type of backup power is a motor generator. Generators have automatic controls that cause them to produce electricity when commercial power is interrupted and are typically fueled by diesel, natural gas, or propane. The actual backup system employed should be determined based upon a risk management assessment of the facility, region, and resources.

Dual fuel generators that can run on more than one type of fuel (*e.g.*, natural gas, propane) provide a high level of flexibility for fuel supply sources. Manual transfer switches in addition to the automatic transfer switches can be installed to allow for set up of quick disconnects which enable portable generators to be brought in and connected in a matter of minutes. Each outage scenario and desired outcome needs to be evaluated in advance to ensure expected infrastructure is in place. For large repositories, risk assessment exercises will inform the decision to have one large generator or multiple smaller ones to support the facility.

Based on risk tolerance assessments and financial stewardship, it may be determined that a backup generator support only designated pieces of equipment deemed critical.

Best Practice: A generator should have a fuel supply to run continuously for a minimum of 48 hours and preferably a minimum of 72 hours, with an ability to re-fill fuel storage supplies.

Best Practice: Repositories that utilize generators should have an established plan for sources to replenish fuel supplies in case of an emergency. This plan should include lists of suppliers and backup suppliers committed to provide the fuel as needed.

Best Practice: Repositories should contact suppliers to be placed on a list as an entity that receives a quick response should an emergency situation arise.

B5.2.1. Generator Tests

To ensure the likelihood that backup power systems function reliably when needed, they should be routinely tested to ensure that the system starts on demand and carries the required load. Load tests should be performed to ensure that the generator functions within specifications under full load. Additionally, for facilities that have bulk diesel storage, annual testing and filtering of the fuel should be performed to ensure that excessive water or bacterial build-up, which can affect performance of the generators, has not occurred.

Best Practice: The power generator system should be included in a frequent preventative maintenance plan which includes weekly testing for automatic starting and power generation and monthly load testing. If load testing places sensitive equipment at risk, the generator should be tested less frequently. Those systems that have an automatic transfer switch should also be tested on a periodic basis (*e.g.*, every six months).

Best Practice: Repositories located in or associated with larger facilities (*e.g.,* hospitals, universities) that automatically initiate backup power upon power interruption should link their freezers and other essential equipment into these emergency systems. The operational safety and testing should be performed by professional caretakers of the larger infrastructure.

Best Practice: For large facilities, staging of the sequence of start-up of mechanical freezers and other systems should be considered to ensure sufficient downtime to allow the compressors to come to rest before restart.

Best Practice: Generator-dependent systems should be periodically checked to confirm automatic restart when the electric power fails. When possible, an attached alarm system (SMS, email, phone call, etc.) should be in place to manage the emergency response.

B6. SECURITY AND ACCESS

Repositories should be equipped with a system that adequately limits access to appropriate staff and protects against physical intrusion from unauthorized individuals. Only persons assigned to repository operations should have access to the material stored within and records of access should be maintained. Freezers or environmental storage equipment that store valuable or sensitive specimens should be individually locked.

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B6.1. Security Systems

Every repository should employ basic security systems to ensure protection of the specimens and data stored therein. A responsible individual should be available at all times to take the necessary action(s) to respond to an alarm in a time frame that prevents or minimizes loss or damage to the stored materials. Systems should initiate calls to other staff trained in emergency response when the first individual fails to acknowledge the alarm.

Best Practice: Repository security systems should be monitored and personnel available to respond to alarms twenty-four hours per day and seven days per week.

B6.2. Intrusion Detection Systems

When either the repository or the building in which it resides is not occupied by authorized personnel, a system should be in place to detect unauthorized entry. Motion detectors, glass break sensors, and door entry sensors should be integral components of the system. As appropriate, the system should accommodate changes to security codes and keys when individuals leave the organization.

B6.3. Visitor Access Policy

An access policy should be developed for individuals visiting the repository. Where feasible and appropriate, sign-in sheets or log books should be used to record the name and affiliation of the visitor, purpose of the visit, as well as track the time at which the visitor(s) enters and leaves the repository. Badges can be made available for the visitors that clearly indicate to staff that they have been formally received and their presence *documented*. Visitors should be accompanied by staff at all times during their visit.

Best Practice: Written or electronic records of repository visitors should be maintained and the records maintained and archived according to the repository's records management practices.

B7. FIRE PREVENTION SYSTEMS

In many countries and municipalities, a fire prevention system is required by building codes for newly constructed facilities and compliance with codes is usually required if a facility is being converted or renovated.

B7.1. Fire Prevention Plan

Repositories should have a written fire prevention plan. The plan should address procedures for regular maintenance on equipment used to prevent or control sources of ignition or fires and name or job title of employees responsible for maintaining the equipment.

Best Practice: The fire prevention plan should include a list of major fire hazards, potential ignition sources, proper handling and storage procedures for hazardous materials, and the type of equipment necessary to control each major hazard.

B7.2. Detection Systems

Automatic fire detection systems are used to quickly identify a developing fire and alert occupants and emergency response personnel before extensive damage occurs. Automatic fire detection systems do this by using electronic sensors to detect the smoke, heat, or flames from a fire and provide an early warning. Fire detection systems should be tested regularly to maintain proper reliability and operating condition by a trained person knowledgeable in the operations and functions of the system. Fire detectors should be selected based on the burning characteristics of the materials present and the nature of location they will be used to protect.

B7.3. Fire Extinguishing/Suppression Systems

B7.3.1. Sprinkler Systems

The most common type of fire suppression is a sprinkler system that sprays water upon activation. The standard system has water in the pipes at all times. Excess heat causes the system to activate, spraying water into the area.

When computer equipment and electrical systems are in place, a "pre-action" sprinkler system can be employed. In such a system, the sprinkler pipes are dry until a fire is detected. This type of system prevents water damage from accidental activation of the sprinkler system. Special consideration should be used if sprinkler systems are deployed in proximity to cold rooms where slip hazards could be an issue.

B7.3.2. Non-Water-Based Fire Retardants

Due to the nature of certain equipment and stored materials, water may be an unsuitable tool for fire suppression. In these instances, other chemicals may be employed. The chemicals used in these systems generally smother the fire by cutting off the supply of oxygen. While these systems can be very effective and may be critical for valuable *collections* adversely affected by exposure to water, they are costly and may present *safety* hazards. Although the majority of these suppressants do not represent a health risk to staff upon activation, personnel should receive appropriate safety training.

Most facilities provide dry chemical fire extinguishers. The suppressant is somewhat corrosive. If used in proximity of mechanical freezers, the dry chemical released can be pulled into the compressor area and damage the unit. There is also risk of specimen contamination as it is difficult to fully remove and clean up the powder in these areas. Other methods such as nitrogen gases may be considered to extinguish fires. Local authorities should be contacted to provide input into any restrictions for the methods that may be employed.

Best Practice: Use extinguishers that contain a non-corrosive gaseous suppressant in repository areas.

B8. EMERGENCY PREPAREDNESS

B8.1. Emergency Response Planning

An emergency response plan should be a component of the disaster recovery plan. Emergencies can cover a wide range of natural and man-made disasters, all of which may have varying effects on the facility and on the ability of the repository to carry out its essential functions. The type and duration of disasters may depend on the geographic location at which the repository is located. Depending on the "value" and the ability to replace certain samples, some repositories may decide to divide collections and store them in different environmental storage *containers* or even at different geographic locations so that a disaster affecting one component of the collection would not eliminate the entire collection.

Repositories should have a written disaster recovery/*incident* response and business continuity plan for responding to a wide variety of emergency situations. This plan should be tested periodically (*e.g.,* at least annually) to ensure that all personnel are trained and that the plan meets the anticipated needs. Copies of these plans should be distributed to all appropriate staff.

Key individuals should be identified who will serve as being "on call" or who will be able to respond to an emergency at the repository. Leave and vacation schedules should be monitored to ensure that coverage of essential responsibilities is in place should key individuals be unavailable. Emergency contact numbers should be posted in prominent locations in the repository and should be carried by staff members at all times who are "on call". The contact information should be reviewed on a regular basis to ensure that the information contained therein is current.

Best Practice: The Director or appropriate staff member should communicate with local power providers before an emergency occurs to request that the repository be placed on a list of "high priority" users for power restoration following an emergency.

Best Practice: Repositories should have a checklist of activities for "on call" staff to follow during an emergency. "On call" staff should be familiar with the location and operation of certain key equipment and controls (*i.e.,* circuit boards) that may need to be checked during an emergency. Telephone numbers for professional assistance should be clearly posted in the repository and accompanying administrative areas (*e.g.*, engineering or facilities personnel, power companies, fuel supply companies, transportation services).

Best Practice: Notification of security and environmental monitoring systems should be verified on a routine basis. Where possible, emergencies should be simulated to ensure proper follow-through for the established emergency plan.

Best Practice: If repository inventory systems are housed on a server located away from the repository, some consideration should be given to storing electronic inventory records on site to ensure that needed records are accessible in an emergency.

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Best Practice: In the event of an impending need for evacuation, repositories that utilize liquid nitrogen bulk tank(s) should arrange to have them filled.

Best Practice: Duplication of specimen collections and data in distinct locations (*e.g.*, including in different freezer units) is recommended to ensure preservation of the holding in the event of a catastrophic event.

B9. PEST AND CONTAMINATION CONTROL

Insects, rats, or other small animals may invade the repository space, for example, through drainage systems, windows, etc. The invasion pathway(s) need to be blocked and an extermination company can be used to help with problem areas.

Consideration should be given into monitoring mold and mildew contamination in high-humidity areas (*e.g.*, facilities and controlled storage environments). A remediation plan should be established to address any contamination issues that arise.

Best Practice: A plan for effective and environmentally sensitive approaches to pest and contamination management should be maintained.

B10. RELOCATION OF A REPOSITORY

There are times that require repositories to relocate from one site to another. Such situations may be caused by the inability to renew a lease if repository space is leased, because the special requirements have changed either due to expansion or reduction of the collections housed within the repository, or due to an emergency situation. Since many considerations must be made to ensure an orderly transfer of equipment and supplies, planning should begin as early as possible to ensure the effective transfer. In preparation for an unanticipated emergency, a plan should be in place and tested in advance to ensure successful implementation. Consideration should be given to whether the repository has sufficient staff and resources to conduct the relocation independently or if a commercial vendor providing such services should be utilized.

The requirements for the new space should be well-documented and complete and should meet the anticipated growth for the period of time for which it will be occupied. Stakeholders and staff should be included in discussions to ensure that all details are attended to and that all training needs are met for handling the collections in the new location.

Relocation should be planned over a period of time that will allow for effective responses to any challenge that may arise. Empty environmental equipment for all storage temperatures reflected in the collection to be transported should be operational and stabilized to receive specimens in the event of a failure of a particular unit during transit. When dry ice bins or shippers are used, careful planning is needed to ensure the temperature and safety of the specimens is maintained during transport. Equipment maintenance professionals should be alerted to the date and time of the move to ensure the likelihood of their rapid response. To the greatest extent possible, repository staff should ensure that shippers, carriers, and drivers follow all regulations for movement of hazardous and infectious materials.

Best Practice: A map should be created for the new site that will indicate the location of all equipment and materials that will be transferred prior to the initiation of the move.

Best Practice: Planning should include review of current processes to ensure that they can be efficiently implemented into the new space.

Best Practice: When planning a large relocation, a mock or pilot relocation run (*e.g.*, a partial movement of the back-up systems of freezers and liquid nitrogen tanks) should be conducted in advance of the actual move to test the plan and make any necessary adjustments.

Best Practice: When large shipments are planned or repositories are relocated, the time of year and environmental conditions (*e.g.*, seasonal weather) should be considered to ensure the safe transport of the specimens and maintenance of *cold chain*.

Best Practice: The details of how the relocation is to be accomplished (*e.g.*, a description of the plan, timelines, roles of staff and contract support) should be documented to ensure that those involved are fully aware of schedules and costs and that the transition process is carried out effectively and appropriately.

Best Practice: Potential impacts of relocation on specimen quality should be recorded and documented.

SECTION C: STORAGE AND PROCESSING EQUIPMENT

C1. GENERAL

The variety of storage systems available for specimen *collections* continues to increase as technologies advance. Storage equipment selections should be based on the type of *specimens* and/or *samples* to be stored, the anticipated length of time the specimens will be stored, the intended use for the specimens, and the resources available for purchasing the equipment. Also important are the size and physical design of the *repository* and the number of specimens stored (as well as predictions for future growth in number of specimens stored). Some freezers and refrigerators now provide automated *specimen* entry and *retrieval* components which may reduce long-term costs for the repository and will maintain specimen quality more effectively as warming events of specimens can be avoided. Often these larger systems are accompanied by increased initial costs, which may be more than smaller repositories can support financially. Equipment selections should take into consideration staffing requirements, *quality* issues, estimated length of specimen storage, available resources, and equipment support and maintenance.

As costs for maintaining repositories have continued to rise, every effort should be made to keep the costs for operating equipment to a minimum. Recent developments in energy-efficient equipment can generate significant savings on facility costs. Several manufacturers are making use of compressor systems that are cooled either by water, where available, or by placing condensers on the exterior of the building so that the heat released from equipment does not have to be counter-balanced by heavy Heating, Ventilation, and Air Conditioning (HVAC) requirements. In addition, there are now freezers with free-piston technology that utilize less energy than compressor-based systems and reduce electric utility costs, heat output, and HVAC cost of operations. These systems may also be introduced into existing facilities that tend to have warmer indoor temperatures, without the need to modify HVAC systems. Energy-saving storage solutions are being introduced to repositories that allow for ambient storage for some material types, eliminating the need for maintaining low-temperature storage environments to ensure specimen integrity (C7. Ambient Temperature Storage). Repositories located in areas where humidity is high (*e.g.*, coast, etc.) should employ a de-humidification system to maintain the preferred storage conditions and minimize the effects on the storage units.

Temperature mapping is performed to ensure that specimens are correctly handled and stored within their specified temperature range(s) and may include freezer rooms, cold rooms, and temperature-controlled storage areas. It is the process of mapping the differences and changes in temperature that occur due to influences like opening doors, proximity to cooling fans, personnel movement, and the quantity of materials being stored at any given time. Temperature mapping locates the points of greatest temperature fluctuation and difference, analyzes the causes of these, and creates 'worst case' conditions to verify that a system maintains the correct temperature levels in all situations when influenced by external factors such as weather, and internal factors such as airflow restrictions and the operation of the HVAC systems (see Appendix A: Internet Resources).

Best Practice: Repositories should have backup power and/or alternate cooling systems in place, as well as an emergency response plan (see Section B8.1. Emergency Response Planning).

Best Practice: Systems should be equipped with redundant compressors that operate under an electrical alternating control system.

Best Practice: Adequate signage should be used for appropriate storage.

Best Practice: To prepare for the possibility of freezer contamination by blood or other fluids, decontamination equipment and procedures should be available in advance.

Best Practice: Oxygen monitors/alarms should be used when liquid nitrogen, liquid CO_2, and/or any other oxygen-depriving compressed gases are used.

Best Practice: Temperature mapping should be performed to document and control the temperature distribution within a storage area upon installation and periodically at defined intervals.

C1.1. Personal Protective Equipment

Normal laboratory personal protective equipment (PPE) (*e.g.*, closed-toed shoes, full cover of legs and feet, goggles) should be worn when handling coolants. The use of protective equipment, goggles, and gloves should be mandatory when handling cryogenics and the equipment should be placed in an easily accessible and visible location. Appropriate outerwear and shoes should be considered when working in walk-in systems that are maintained at cryogenic temperatures. Appropriate training in the safe handling of

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cryogenics should be provided and included in an SOP, describing the potential health hazards and required *safety* precautions. Additional information about PPE can be found in Section F5. Personal Protective Equipment.

C.1.2. Identification of Specimen Storage Containers

The type of *label/identifier* utilized should be appropriate for the storage equipment and needs to be able to withstand the temperature conditions of the system. A unique human-readable identifier that can be read electronically (*e.g.*, barcode, Radio-Frequency Identification [RFID]) should be on each specimen *container*. The container and identifier should meet the needs of the downstream processes and *end-user* demands. See Section I2.13. Labels for additional information.

A pre-approved test plan for validating labels/identifiers should include evaluation for readability, ability to scan, stability of the identifier over time, etc., at the storage conditions used in the repository as well as known downstream applications (*e.g.*, heat blocks, water baths, xylene, alcohol). Given there are low-cost solutions to identify and track specimens, hand labeling is not recommended, as it is not compatible with automation or best practice given issues with legibility, permanency, etc. (see Appendix A: Internet Resources).

Best Practice: The use of barcodes (*e.g.*, 1D, 2D) is highly recommended to ensure accurate tracking of specimens.

Best Practice: The particular type of label should be evaluated for its performance over a variety of conditions prior to use.

C2. LIQUID NITROGEN STORAGE SYSTEMS

The use of *liquid nitrogen* (LN_2) for long-term specimen *preservation* is optimal for the storage of some types of biological material. Cryogenic storage using LN_2 is an effective long-term storage platform because on-site LN_2 supplies reduce reliance on mechanical freezers that use electrical power, especially in areas where power is unreliable and LN_2 is available.

Technological advances have led to the development of new systems that allow specimens to be handled either fully or semi-automatically while stored in the vapor phase of liquid nitrogen. Such systems provide areas for handling and *retrieval* that are cooled to ultra-low temperatures (below -100°C) preventing cooling/re-warming cycles of the specimens.

When considering storing in LN_2 vapor phase (≤ -150°C) vs. submersion in liquid phase (-196°C), vapor phase storage is preferred because it provides sufficiently low temperatures to maintain specimens below the *Tg* (*Glass Transition* Temperature; -132°C) while avoiding contamination issues and safety hazards inherent in liquid phase storage. At temperatures below -132°C, the extreme cold arrests biological life and slows most chemical and physical reactions that cause specimens to deteriorate.

While LN_2 storage has been traditionally reserved to *containers* that either hold LN_2 in the base of the freezer or which hold enough liquid for specimens that are submerged in LN_2, equipment is now available that allows for LN_2 to be used as a coolant to allow for storage temperatures in the +4 to -80°C range. This type of cooling may have the advantage of being able to maintain the temperature of specimens in the event of a power failure. A comprehensive assessment of available choices in equipment design should be made prior to making any new purchases.

Best Practice: Any storage unit used at cryogenic temperatures should be rated for these temperatures and have relief valves to evacuate over-pressures.

C2.1. Specimen Storage Containers

The liquid to gas expansion ratio of LN_2 is 1:696 when brought to a gaseous phase at room temperature[1]. This situation may produce an explosion hazard. Glass, metal, and some plastic specimen containers (*e.g.*, vials, tubes, straws) can crack and/or explode if LN_2 is trapped inside the specimen container when it is removed from the freezer. Certain containers, like cryogenic straws, are hermetically sealed and specifically designed for the safe storage of specimens in the liquid phase of nitrogen.

Best Practice: Specimen containers selected for storage in LN_2 should be tested prior to use given many commercially available specimen containers are penetrable by liquid nitrogen and can create an explosion hazard.

C2.2. Liquid Nitrogen Supply

Where LN_2 refrigeration is employed, an adequate supply of LN_2 should be maintained. For freezers filled from *Dewars* or supply tanks, a minimum three-day supply of LN_2 at normal usage and replenishment intervals should be maintained, with the assumption that a re-supply is readily available. Bulk supply systems should maintain at least three days' working capacity. Bulk supplies should be checked for re-supply at least once a week. A *telemetry system* may be installed to allow suppliers to monitor liquid levels in real time to ensure stocks do not drop below agreed-upon levels.

Bulk storage and piping systems require relief valves to prevent rupturing of the pipe and bulk tanks in the event of over-pressure. If relief valves trip unexpectedly, a person near a valve can be sprayed with either the cold gas or the liquid. More likely, in the event of a blockage or excessive pressure, several relief valves may vent nearly simultaneously. This can cause a "whiteout" condition in a matter of a few seconds. Visibility can drop to near zero and oxygen levels in the area may become less than that necessary to sustain life. Under these circumstances, personnel should evacuate immediately. For this reason, O_2 monitoring should be installed in any areas of the facility where LN_2 is utilized (See Section C2.5.1. Oxygen Sensors).

Best Practice: Daily LN_2 usage per freezer should be recorded either by monitoring the display levels or by manual means as excessive LN_2 usage can indicate problems with the vacuum component of the freezer.

C2.3. Liquid Nitrogen Safety

Additional safety precautions are needed when utilizing LN_2 freezers given the displacement of oxygen and extremely cold temperatures pose increased risk to personnel compared to other freezer systems (see Section F6.8. Liquid Nitrogen Safety).

C2.3.1. Oxygen Sensors

Because nitrogen displaces oxygen, care should be taken when LN_2 freezers are employed. The risk is inversely correlated with the size of the room. Oxygen level sensors should always be employed when LN_2 freezers are used in a repository. Normal levels of oxygen in ambient air should be ~21%. Most installed oxygen sensor units have batteries or sensor cells that should be replaced and re-calibrated as directed by the manufacturer. Consult the manufacturer for recommended requirements to determine the number of sensors needed based on the size of the room, to confirm the placement in the room, and height of wall mounting. Acoustic and visible alarms may be installed in and out of the room and dedicated exhaust ventilation may be used in coordination with the sensors. Rooms with LN_2 freezers should have viewing window(s) to determine whether it is occupied during alarms.

Both fixed and mobile/personal monitors may be appropriate depending on the size of the facility. Even when installed units indicate an alarm condition, it may be useful to employ a personal monitor to enter the room carefully to validate the alarm condition if the area is not visible from outside the room. It may be more appropriate to use mobile oxygen monitors in a secure area where LN_2 freezers operate because the sensors in installed units will degrade over time and sound false alarms.

Best Practice: All monitoring systems for measuring oxygen deficient atmospheres should be installed and evaluated per the manufacturer's instructions. Staff should carry personal oxygen monitors when safety conditions warrant it.

Best Practice: Duplicate systems (*e.g.*, wall system, automatic emergency fans, automatic door opening, personnel monitoring system) should be employed to ensure the highest level of personal protection.

C2.3.2. Personal Protective Equipment

In addition to the oxygen deficit risks described under Section C2.5. Liquid Nitrogen Safety, use of LN_2 as a refrigerant poses special safety problems because of its low temperature and rate of expansion when placed at ambient conditions. Eye protection is mandatory every time LN_2 is handled to protect against splashes that inevitably occur. Face and eye protection is recommended when handling vials removed from a LN_2 freezer or when dispensing LN_2 from low-pressure lines. Heavy gloves (appropriate for LN_2 use) should be worn to protect hands

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when handling specimens stored within the liquid phase or when transferring LN_2 or other coolants to Dewar flasks.

C3. MECHANICAL FREEZERS

Mechanical freezers are employed in a variety of storage temperature ranges and come in a wide variety of sizes, configurations, and electric voltages. Because these are devices attached to commercial power systems, a back-up power plan and emergency response plan should be in place (see Section B8. Emergency Preparedness). The length of time that results in the significant warming of the stored material will vary by the properties of the stored material, the temperature of the material stored in the freezer, the ambient conditions, and the design and maintenance of the unit. Chest systems maintain better cold retention upon opening while uprights typically provide more efficient compartmentalized storage. It is the responsibility of the facility operator to establish and enforce the critical temperatures and response times to alarms.

Some mechanical freezers are equipped with emergency backup systems that automatically cool their contents with either LN_2 or liquid carbon dioxide (CO_2) in the event of an extended power loss. Any freezer implementing this type of emergency backup cooling system should be specifically designed to accommodate whatever coolants are utilized and adequate supplies of refrigerant gas should be kept on hand at all times to operate the system. Safety precautions with the backup system (O_2 or CO_2 monitoring systems) should be taken into consideration in the event of an emergency. Precautions should be taken to maintain the safety of personnel in the areas where compressed gases such as CO_2 or LN_2 are used (see Section F6.2.2. Compressed Gases).

Independent of backup cooling solutions, efforts should be made to ensure that freezers (as well as refrigerators) are positioned in repositories to allow for adequate airflow. Insufficient distance between units or between units and walls may lead to overheating of compressors, shortening compressor life. In addition, inadequate air circulation may lead to the growth of mold and other harmful microbial contamination situations. HVAC systems are more efficient than simple ventilation systems at maintaining temperatures and humidity.

A cascade freezer system is a series of storage units that are connected to a central cooling unit. The benefit of cascade systems is greater storage capacity in a smaller footprint with greatly reduced energy consumption over stand-alone units. In addition, the mechanical cooling systems may be placed in areas external to the *sample* storage reducing heat and noise in the storage/work area. The upfront cost is typically greater than stand-alone units, but the reduced footprint and energy consumption can pay for this upfront cost over time in the right situation. Cascade freezer systems are available in a wide variety of configurations, including size, number of chests, temperature ranges, and voltage requirements. The systems should be designed with full redundant cooling systems to mitigate failure and allow for maintenance of the system while online. The systems can be scheduled to run in alternation so that both units do not wear out at the same time. The system can be configured with one or multiple chest or upright configurations. A typical installation example can have ten storage units with the capacity of 30 stand-alone, large, uprights in less than half of the area. A cascade system should be configured with the ability to manually control cooling and to isolate individual containment areas, as well as the ability to replace individual storage units if possible. It is recommended to have independent alarms systems for the units and it is the responsibility of the facility operator to establish and enforce the critical temperatures during access of the individual units and response times to alarms.

C4. AUTOMATED STORAGE SYSTEMS

Automated specimen storage and retrieval systems keep specimens at their required storage temperature while minimizing temperature fluctuations. It is important for the specimen storage temperature and the specimen retrieving temperature to be as close as possible to prevent warming events. Other considerations for the use of automated specimen storage are the specimen tracking capability, *audit* trail, and maximization of the storage capacity. Most systems can consolidate empty positions of stored racks (defragmentation). Some systems provide the ability to store multiple labware types.

Automated specimen storage solutions are available in various temperature settings (*e.g.*, ambient, -20°C, -80°C, and -150°C) and various size solutions for collections ranging from thousands to millions. Many systems can be expanded as the collection grows. In addition, most automation systems have lower energy requirements, smaller footprints, and require lower HVAC output than individual storage units.

C4.1. Specimen Storage Containers

The first step in considering automation of any repository should be the labware type utilized.

The choice of labware size and manufacturer is optional, but at a minimum, a unique identifier that can be read electronically (barcode, RFID, etc.) should be on each specimen as many downstream processes can only be automated if the specimens have a barcode label. Although this may be a more expensive option, legacy collections without these barcodes are not automation friendly. Hand labeling is not recommended as it is not compatible with automation or best practice given issues with legibility, permanency, etc. See Section I2.13. Labels for additional detail.

C5. REFRIGERATORS

Refrigerators are commonly employed where the longevity of the material being stored is enhanced by storage below ambient temperature. This is the preferred storage medium when the material should be kept cool but does not require freezing. Refrigerators may also be used for short-term storage of media and additives based on expiration dates. It is important to ensure that the temperature is maintained within the specified operating range, not just below a maximum temperature. Some high value materials should be maintained precisely between 2°C and 8°C.

C6. WALK-IN ENVIRONMENTAL STORAGE SYSTEMS

C6.1. Design

Walk-in refrigerators and freezers should be equipped with redundant compressors that operate under an electrical alternating control system. It is important to consider noise reduction strategies when employing units with compressors. To decrease the noise in the rest of the repository, it may be important to isolate the compressors in their own enclosure within the facility. Rusting of the metal parts in freezers can be a serious issue during long-time storage. Care should be taken to reduce the moisture content of the air inflow to freezers in high-humidity environments.

When evaluating whether to use mechanical or walk-in freezer systems, a consideration in the decision-making process is the lower cost of operation of walk-in freezers compared to stand-alone mechanical freezers. In addition, most walk-in systems have lower energy requirements, smaller footprints, and require lower HVAC output.

Best Practice: To inhibit the rusting of metal parts, repositories should apply anti-rust coatings and install-dehumidification systems.

C6.2. Safety

In most countries building codes require that walk-in units have internal safety releases to prevent a person from being trapped within a unit by the accidental closing of doors (*e.g.*, interior door release mechanism). Because of the special hazards involved in personnel working in a -20°C or colder walk-in environment, it is desirable that some form of monitoring system be employed and that consideration is given to the amount of time it is safe to work inside the system. This is especially applicable if only one person is working in the freezer; however, most repositories employ a buddy system. Multiple technologies to detect motion of personnel working in the system are available such as wearable devices commonly employed by firefighters and other emergency personnel or motion detectors permanently installed in the system. Walk-in freezers should be kept free of *dry ice* (*i.e.,* the solid phase of CO_2). Carbon dioxide can rapidly build-up, displace the oxygen in the room, and cause personnel working in the units to lose consciousness. Where dry ice is employed, there should be adequate ventilation to ensure that sufficient air or oxygen levels exist. In these circumstances, it is recommended that walk-in freezers have both oxygen and CO_2 monitors as well as an automatic emergency exhaust fan. Similarly, it is not appropriate to use scientific cold rooms to store hazardous or flammable material or food.

Moisture within walk-in systems can generate slipping and falling hazards if water condenses on the floor. Freezers can occasionally create ice or water on the floor if the unit is defrosting. Some type of rubberized mat or grate should be placed in front of these types of units to prevent slipping.

Best Practice: For a -20°C or colder walk-in environment, engineering controls may be designed to support an audible alarm system coupled with a safety *procedure* to allow for the safest operating conditions.

Best Practice: A warning sign should be posted at the entrance of walk-in cold storage areas advising that the area may be slippery.

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C7. AMBIENT TEMPERATURE STORAGE

While formalin-fixed, paraffin-embedded (FFPE) tissues have been stored at room temperature for centuries, recent developments have allowed for the identification of biological storage matrices that allow for long-term maintenance of additional biological components at room temperature. These matrices have been used for the storage of dry blood spots, isolated RNA and DNA, and for other biological materials. They may be helpful when mechanical or cryogenic equipment is not available or may serve as an alternative method for backup storage for some material types[2]. Prior to implementation, all matrices should be evaluated to be sure that they are appropriate for downstream purposes and applications. See also Section E1. Validation of Sample Processing Methods.

Storage cabinets for ambient temperature storage of specimens can be equipped with passive or active humidity controls. These storage cabinets can be fully integrated with automation and robotic controls as well as tracking and specimen management software.

C7.1. Storage of FFPE Tissue Blocks and Slides

FFPE tissue blocks and slides are stored in a variety of ways. Many are stored in cabinets or other manual storage systems. This includes manual placement, sorting, and retrieval of tissue blocks and slides. Sorting of specimens should be done chronologically or study-based to ensure the increased efficiency of locating the specimen. It is a good idea to place a marker in the position of the removed specimen to allow ease of returning the specimen to the original location, when appropriate. Regardless of the storage system used, FFPE specimen storage at room temperature (20 – 25°C) should be in a controlled low-humidity environment[3].

Manual handling of FFPE specimens is associated with major drawbacks, including: (1) manual labeling of specimens can be ambiguous and may lead to misidentification; (2) returning a specimen to a different storage location can lead to "disappearance" of the specimen; and (3) difficulty in controlling incoming and outgoing specimens, may result in challenges in running a proper *database* of specimens stored in the archive.

New technologies for automating FFPE storage are being developed. Semi-automated systems using barcoded blocks and slides (2D barcodes are preferred) not only reduce the work load of the repository personnel but also increase the reliability of inventory control by scanning of each incoming and outgoing specimen. It is recommended that automation be implemented when either collection size or activity level increases to the point where efficient retrieval and organization become a bottleneck to the repository.

Best Practice: FFPE blocks stored at room temperature (20 – 25°C) should be under controlled low humidity.

Best Practice: Specimen quality is maintained optimal when the FFPE blocks are stored at -20°C to 4°C. Repositories should validate the fitness-for-purpose of the paraffin they use to sub-zero temperatures.

Best Practice: Barcodes (*e.g.*, 1D, 2D) should be used to ensure accurate tracking of FFPE specimens.

C8. CONTAMINATION ISSUES

Every effort should be made to avoid contamination of specimens. Contamination by fungus can frequently develop in cold storage rooms (2 – 8°C), refrigerators, or at ambient temperatures. It is important to periodically survey areas to eliminate factors (*e.g.,* damp, unclean areas, cardboard boxes) that can facilitate fungal growth. Periodic monitoring should be encouraged to visually monitor for fungal contamination and for items that may be inappropriately stored. Repositories should consider the use of dehumidification systems.

C9. BACKUP STORAGE CAPACITY

Adequate backup capacity for low-temperature units should be maintained in anticipation of possible equipment failure. If space and funds allow, backup storage for each storage condition should be available within the repository. Where this is not possible, repository staff should identify backup space in a nearby facility to allow for transfer of specimens in case of an emergency. When colocation is not possible, LN_2, dry ice, and/or portable freezers should be available at the facility to maintain specimens during transfer to the backup units offsite in the event of an emergency. Additional backup power should also be available. Refer to Section B: Facilities for additional

details on emergency preparedness and relocation of a repository.

Best Practice: Extra-capacity equipment should be equal to the capacity of the largest single storage unit and should be maintained in reserve at operating temperature. The total amount of backup storage required for large repositories should be determined empirically.

Best Practice: Repositories should have a written procedure for transferring specimens from a failed or malfunctioning unit (one that has exceeded or is on the verge of exceeding its acceptable operating temperature range or become over-filled) and for the return of the specimens to their original location once it is considered safe to do so. The procedure should include the freezer or refrigerator name or number as well as the location within the freezer where the specimens have been relocated.

C10. ENVIRONMENTAL MONITORING SYSTEMS

Acceptable temperature ranges should be determined for any specimen storage equipment that is designated for operation at a specific temperature before the equipment is put into service. Temperature ranges allow for normal operating variations and provide some variation for warming when the material is accessed. It is important to understand that temperature probes measure the temperature where the probes are located; therefore, different locations in the equipment might exhibit different temperatures depending on the size and age of the unit as well as other factors. Also, note that freezers and refrigerators that are full will likely display temperature readings that are different from readings taken when the equipment is empty.

Once placed in service, daily and continuous monitoring practices and systems should be used for evaluating the performance of all fixed-temperature storage units. Storage units with defined environmental conditions should have temperature-monitoring devices that can be visually inspected on a regular basis.

In addition to regular temperature-monitoring activities performed by repository staff, an automatic temperature-monitoring system should be utilized that continually monitors temperatures of all critical equipment and other important parameters, creates logs, generates *audit* trails, and generates alarms to notify personnel trained in emergency preparedness to respond. An option to have an audible alarm for those individuals physically present in the repository can be beneficial as well.

The alarm notification system should call or page the individual "on call" (or should activate the "on call" list) rather than simply providing passive notification (*e.g.*, provide computer-generated notification which has to be monitored by staff; see also Section B6.1. Security Systems).

Depending on the size of the repository and number of staff available, more than one individual should be available at all times, in case the first individual is in a location where he or she cannot receive or respond to the notification. Alarm conditions should be responded to in a timeframe that minimizes the likelihood of damage to the stored material. Repository management should ensure that personnel with adequate training who can take corrective action should be available or reachable 24 hours per day, seven days per week (see Section C12. Equipment Maintenance, Repair, and Replacement).

One additional method for automated temperature monitoring involves the connection of thermocouple wires from the "dry" temperature contacts to the building security system that allows identification of individual storage units in alarm.

Visual inspection of room and storage equipment temperatures should be performed regularly (at least three times a week) and a record kept of the temperatures observed. Temperature records should be verified monthly by supervisors. In addition to monitoring the current room and storage equipment conditions, regular recording and review of temperatures (preferably daily) provides a way to spot trends, which may provide an indication of degraded performance or incipient failure.

Temperatures should be monitored during extended periods of freezer access to ensure that safe temperature ranges are not exceeded. Attention should be given to the fact that closing the freezer or refrigerator warming may not immediately reverse warming.

Best Practice: Environmental monitoring systems should be qualified prior to and periodically during use as required by business need (also see Section C12.2. Verification of Equipment Functionality).

Best Practice: In repositories where specimens are stored in the vapor phase of liquid nitrogen, staff should regularly employ a technique whereby a physical measurement of the liquid nitrogen level is taken with a tool such as a dipstick to confirm the liquid nitrogen level. Alternatively, probes may be placed at various levels in the freezer to monitor liquid nitrogen levels (*e.g.*, temperatures below 196°C indicate that the probe is submerged in liquid nitrogen and temperatures warmer than -196°C indicate that

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the probes are in the vapor phase of the chamber). If a tool is used to measure liquid levels, it should be treated with ethanol, bleach, or other *disinfectants* to disinfect the tool before and after it is used.

Best Practice: Alarms should be tested on a regular basis (*e.g.*, weekly or monthly) to ensure proper functioning and call-out to pagers and other notification devices used by staff that are "on call".

Best Practice: In repositories that use an automated *environmental monitoring system*, periodic review of temperature profiles or trends should be employed to ensure consistency between the controller display values and the environmental monitoring system values. This practice will allow staff to proactively evaluate each unit's performance and determine if any maintenance work is needed.

C11. AUTOMATED LIQUID-HANDLING ROBOTICS

Automated liquid-handling robots can provide increased throughput, improved precision, and fewer errors than manual manipulation and pipetting tasks. Most liquid-handling robots incorporate barcode scanners to accurately track their specimen *processing*. This ensures proper specimen tracking for all downstream processing and applications.

There are two main types of pipetting robots: air displacement and liquid displacement systems. Like manual pipettes, air displacement systems use air/vacuum to dispense or withdraw liquids. The liquid displacement systems use syringe pumps to move liquid through flexible tubing to displace the appropriate volume of the requested specimen. Either system is acceptable if there is a procedure for *calibration* and validation of both the instrument and their associated methods. Methods used to calibrate for accuracy and precision of the pipetting process include gravimetric and spectrographic techniques. These procedures should be done once per year at a minimum and more often based upon the use of the liquid handler.

Automated liquid-handling robots come in a variety of sizes and functionality. Liquid-handling applications that may be performed with automated liquid handlers include blood fractionation (separation of serum, peripheral blood mononuclear cells, red blood cells [RBCs]), nucleic acid extraction, *aliquoting*, DNA normalization, etc. Additional hardware options such as cooled plates, shakers, heaters, and incubators can be included. These systems utilize disposable tips. Filter tips can be used to prevent cross contamination of biological specimens.

Additional automated processing systems which can help assist laboratories in the performance of their daily operations include automated weighing stations, tube sorters, and detection systems for quantification. As with any automated specimen processing system, a validated Laboratory Information Management System should be employed to track and register all specimens being processed. The use of 1D barcodes are required and 2D barcoded tubes are highly recommended to ensure the highest level of compatibility with automation.

C12. EQUIPMENT MAINTENANCE, REPAIR, AND REPLACEMENT

A system for preventative maintenance and repair of storage equipment, supporting systems, and facilities should be in place. System maintenance should be performed at regular, established intervals per manufacturer's recommendation and as determined as *fit for purpose* aligned with the repository's practices. Equipment exposed to infectious (or potentially infectious) materials should be properly disinfected. The choice of disinfectant to be used depends on the situation. Some disinfectants have a wide spectrum (kill many different types of microorganisms), while others kill a smaller range of disease-causing organisms but are preferred for other properties (they may be non-corrosive, non-toxic, or inexpensive). For example, bleach should not be used on stainless steel as it can result in pitting of the metal and damage to the equipment.

C12.1. Calibration

A system for the calibration of all instruments should be in place. Any device that provides analog or digital measurements is considered an instrument and requires calibration. Calibration should be done annually or per manufacturer's recommendation.

Best Practice: Calibration records should include the appropriate standard readings taken both before and after calibration.

Best Practice: A log of calibration records should be kept that includes the date of the calibration, the name of the individual performing the calibration, the name/serial number of the device used against which the instrument is calibrated, and a reference to the standard operating procedure used to perform the calibration.

Best Practice: Instruments used for calibrations should be 'verified' against an approved,

recognized calibrator source (*e.g.*, NIST [National Institute of Standards and Technology]).

C12.2. Verification of Equipment Functionality

The proper performance of all equipment and related software should be verified or qualified prior to use or following repairs that affect the instrument's operating capabilities. Documentation of the testing should be maintained and made available for audits. The repository Director should ensure that all required regulatory practices are implemented.

Best Practice: Freezer and refrigerator units should be qualified prior to and periodically during use by performing temperature mapping with multiple thermocouples placed throughout the storage unit to evaluate consistency of temperature. This temperature profile should be performed prior to its initial use so that warm and cold spots that could be problematic for material storage can be identified.

Best Practice: The entire system should be re-validated when any changes are made to the software and/or automation equipment.

C12.3. Equipment Preventative Maintenance and Repair

Essentially all equipment composed of multiple components wears out with time and exposure to various environmental conditions. Performing routine assessments and modifications to the equipment per the manufacturer's specifications may significantly extend the duration of the lifetime for equipment used in the repository. For mechanical freezers, this may include a periodic changing out of fluids, cleaning of filters, calibration of probes, or manually removing ice from the tops and sides of the interior chamber of the freezer. Routine maintenance recommendations should be determined before a piece of equipment is put into service. Frost-free freezers should not be used for repository storage, since the daily heating cycle built into the doors of these models gradually causes deterioration/*desiccation* of specimens stored near the doors and walls of the unit. Maintenance records should provide a description of the maintenance performed, date of maintenance, and indication of personnel performing the maintenance.

Repair records should provide a description of the cause of the equipment failure (where possible), the date on which the *incident* occurred and was observed (these performed to verify proper functioning of the equipment), and the results compared to available standards and manufacturer recommendations. Equipment taken out of use should be labeled appropriately and the event recorded (include a record of the date when returned to service, if applicable).

Best Practice: Properly trained personnel with expertise in monitoring and repairing repository equipment (especially freezers and refrigerators) should be used for regular and emergency repairs. These trained technicians may be on the repository staff, may be on staff within the larger organization within the institution in which the repository resides, may be available through a "fee for service" arrangement with a commercial entity with this expertise, or repair services may be obtained from a similar entity on a retainer basis.

Best Practice: Repositories should maintain spare parts for critical equipment, especially for aging equipment for which parts may not be readily available.

C12.4. Repair *vs.* Replacement

While most manufacturers of repository equipment offer projections for the expected lifetime of that equipment, actual lifetimes vary depending on a variety of factors including preventative maintenance, availability of replacement parts, environmental conditions in the area in which the equipment is located, etc. For example, manufacturers of mechanical freezers offer projections of lifetimes that range from 8-12 years, but actual lifetimes might run for a period of 5 to 15+ years. Liquid nitrogen freezers may have lifetimes extending through 10 to 35 years.

Long-range plans should be made to address the possible repair and replacement of equipment essential to the functioning of the repository. When multiple repairs are required, the additional cost of making those repairs may lead to a decision to have the unit replaced. Since replacement of freezers and refrigerators can be expensive, it is best to anticipate these costs and have some financial reserves available to address this when decisions to replace equipment are made.

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Best Practice: Repositories should plan for the orderly replacement of equipment. If multiple pieces of the same equipment need replacement at one time, it might be best to use interim equipment or backup equipment while introducing the new equipment in over time. This allows for a gradual introduction of new equipment so that likely repair and replacement schedules are likely to be staggered.

Best Practice: Resources for equipment repair and replacement should be identified when the repository is being established before an emergency is experienced. These resources should be reviewed on an annual basis.

Best Practice: Before new equipment is purchased, an evaluation should be performed to identify the most energy-efficient equipment that effectively addresses the need(s) for that equipment. Attention should be given to the expected life of the equipment (*e.g.,* mean time between failures, experience with the equipment in other installations).

CITATIONSS

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SECTION D: QUALITY MANAGEMENT

D1. GENERAL

The purpose of a *repository* is to supply specimens and their associated data in a form that meets specific *quality* criteria and is provided in compliance with all necessary regulatory and statutory obligations. Therefore, aQMS that includes *Quality Assurance* (QA) and *Quality Control* (QC) programs should cover the full spectrum of a repository's operations. The implementation and maintenance of a QMS contributes to the long-term sustainability of repositories. These systems support the delivery of high-quality services to *end-user* communities and in doing so sustain the business, utility, and research viability of *collections*.

Quality Assurance is an integrated system of management activities involving planning, implementation, documentation, assessment, and improvement to ensure that a process is of the type and quality needed for the project. Quality Control is the system of technical activities that measures the attributes and performance of a process or product against defined standards to verify that the stated requirements are fully met. The QC process also confirms the authenticity of a collection's holdings (*e.g.,* reference strains and cell lines).

Each repository should have a QMS or adhere to the QA program of the organization with which the repository is associated. The program should describe the repository's commitment to its QA and QC programs and describe approaches for ensuring that the requirements of these programs are met. An essential component of quality management is a formal system for documentation and record-keeping (see Sections D4. Documents of the Quality Management System and D5. Records Management).

If it is not possible to have a formal QMS with dedicated staff, then a procedure should be in place to review *documents* and records to assess the efficacy and quality of repository operations. This review should be conducted at least on an annual basis[1,2].

D2. BEST PRACTICES

Best practices are used to maintain quality as a complement to mandated or regulated standards. A best practice is generally accepted as a technique, procedure, or method that produces superior results to those achieved by other means. Best practices are established through experience and research that have been proven to lead to a desired and often evidence-based result. Best practices go above and beyond standard recommendations and may be cost-prohibitive in some cases. Repository management and other staff should decide which practices to adopt that best support their particular circumstances and include it in their SOPs.

D2.1. Relevant Best Practices

- ISBER Best Practices: Recommendations for Repositories
- Consensus Best Practices for Biological Resource Centers in OECD Countries
- Council of Europe Recommendation Rec (2006)4 of the Committee of Ministers to member states on research on biological materials of human origin
- Laboratory Medicine Best Practices sponsored by the Centers for Disease Control and Prevention's (CDC) Division of Laboratory Systems
- National Cancer Institute Best Practices for Biospecimen Resources ("NCI Best Practices")

D3. STAFF RESPONSIBILITIES

Overall responsibility for quality management should be assigned to the Director or Quality Manager whose responsibility is to ensure repository staff are trained to comply with quality standards and to provide regular guidance and instruction to all personnel. All staff should exercise collective responsibility for assuring compliance with SOPs, policies, and regulatory requirements. QMS staff should have the responsibility and authority to inspect and approve specimen handling, *processing*, and storage practices, as well as discontinue processing and/or release of specimens when errors warrant.

A repository should have a clear policy and create a system for reporting, documentation, and follow-up of any *deviation*, *incident*, or failure and personnel should be trained and encouraged to report deviations as learning opportunities supporting quality improvement. QMS personnel should be responsible for implementing both audits and accreditation or certification processes. To ensure consistency across staffing, training, and competency, assessment programs should be established as an important component of any QMS.

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D4. DOCUMENTS OF THE QUALITY MANAGEMENT SYSTEM

A repository should create a series of documents, including a quality manual, which make a clear quality statement and describe the roles and responsibilities of staff within and connected to the repository's operations. The documents of the quality management system ensure that the *biorepository* infrastructure is in compliance with regulatory and *safety* obligations. The quality manual may reference all the procedures which are required to ensure that QA/QC objectives are fulfilled and be commonly accessible in working areas.

D4.1. STANDARD OPERATING PROCEDURES

SOPs serve as the description of how tasks pertaining to repository operations should be handled by staff assigned to those specific responsibilities. SOPs allow for uniformity and reproducibility in specimen handling. SOPs should be written by an individual or group of individuals with experience in successfully performing the processes described and should be managed in a document management system. Draft SOPs should be reviewed before they are finalized. Personnel should be trained in the use of the SOPs which should be reviewed on a regular and routine basis or in response to accidents, incidents, and failure to conform to the QA/QC system.

Essential components of an SOP are listed below:

- Title – a unique name which captures the essence of the practice described.
- Number – a unique number that can be used for easy reference.
- Date – date the procedure was first introduced as well as the date of the most recent version.
- Version Reference – system for tracking version number and/or date to ensure the most recent version is used.
- Department/Division/Staff Covered – individuals to whom the SOP will apply.
- Purpose – brief description of the utility of the process(es) described in the SOP.
- Protective Wear – protective equipment that should be worn by staff when performing the procedure described.
- Equipment – list of the equipment needed to perform the procedure. The SOP may direct the user to maintain a list of equipment(s) utilized by the repository; the equipment record may include but is not limited to the name, model, date of purchase, serial number, asset tracking number, and manufacturer.
- Supplies – all materials and supplies needed to perform the procedure should be recorded. The SOP may direct the user to maintain a record of the vendor, catalog number, lot number, and expiration dates for the materials and supplies utilized.
- Step-by-Step Guidance – the procedure should be written in specific detail to ensure that it can be repeated in a reproducible fashion to include the order of steps that should be followed, the times allowed for each step (as needed), and the temperatures at which the steps are to be performed.
- Safety – describes any safety steps or references to any relevant SOPS and addresses appropriate regulatory compliance (*i.e.*, institution and/or country-specific) associated with the procedures. Careful review and inclusion of Safety Data Sheets (SDS)/Material Safety Data Sheets (MSDS) or similar globally accepted regulation such as the Globally Harmonized System of Classification and Labeling of Chemicals is also recommended (see Appendix A: Internet Resources).

D4.1.1. Implementation

Either the repository Director and/or the individual responsible for the Quality Management Program (*i.e.*, Quality Manager) should review and approve all SOPs and associated *process validation studies* prior to release and implementation. Upon implementation, all SOPs should be followed as written.

D4.1.2. Modifications

Each repository should have document control policies in place that govern document and SOP management including creation, revision, review, authorization, publishing, and archiving. Changes should be clearly marked in the new version of the document versus the previous version. Prior to implementation, each modification should be approved by the Quality Manager or Director. Implementation dates should be recorded for all procedures.

A system should be in place to ensure that only current versions of documents are available for use and that previous versions are removed when new revisions are issued. Old versions of documents should be removed and archived when new revisions are issued.

D4.1.3. Review of Standard Operating Procedures

SOPs should be reviewed regularly to ensure the current policy and/or method for performing the procedure is described. A system should be in place to document the revision number and date of release of the revised document.

Best Practice: SOPs should be reviewed annually and/or when policy or methods change.

D4.1.4. Staff Access and Review

Current controlled copies of the SOPs should be stored in designated locations and available to the staff at all times. New and revised policies and procedures should be read by the staff prior to implementation.

Best Practice: A system should be in place to document staff review of the most recent versions of an SOP.

Best Practice: Training associated with SOPs should be maintained in a training record (see Section G2.7. Training Records).

D4.2. Types of Documents of the Quality Management System

A repository should develop and maintain an *Operating Manual* which contains procedures, instructions, and guidance for use by repository personnel. An Operating Manual should specifically include, but not be limited to, SOPs and other documents regarding the following:

Administrative Policies

- Organizational chart, personnel policies, staff and director responsibilities, delegation of functions, compliance with regulations, and introduction of new personnel.
- Customer relations, forms, and agreement templates.
- Project-specific SOPs (*e.g.*, it is the responsibility of the repository to follow sponsored/investigator initiated studies when it differs from their standard procedures). Conflicts should be resolved.

Specimen Handling

- Collection, labeling, transport, receipt, quality control, processing, *distribution*, and disbursement.
- Shipping and receiving.
- Relocation of specimens within a repository as equipment and environmental needs warrant.
- Laboratory procedures for specimen *aliquoting* or other specimen processing.
- Laboratory procedures for tests performed in-house.
- Where appropriate, human subjects protection documentation, including policies/procedures on *informed consent;* privacy and confidentiality protections; animal welfare-related documents; and other legal, ethical, and cultural issues.
- Procedures on access and sharing of specimens and associated data.
- Where appropriate, procedures on the disposal of specimen of participants who have requested the withdrawal from a study.

Facilities and Equipment Management

- Repository security.
- Maintenance of essential support systems (*e.g.*, liquid nitrogen supplies, electricity, extra power supply, temperature control system).
- Environmental monitoring and alarm systems.
- Equipment qualification, maintenance, repair, *calibration*, upgrading, and replacement.

Quality Assurance (see Section D4.3.)

- Policies for performing validation/qualification of instruments, reagents, *labels*, and processes employed in specimen collection, processing, storage, and *retrieval*.
- Policies for quality metrics, handling non-conformities, performing corrective actions.

Safety

- General safety policies including chemical, biological, and fire safety.

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- Safety programs including documentation of staff *ergonomics*, management of safety-related incidents, injuries and exposure to potential human pathogens, and notifiable animal/plant pathogens and agents under biological control.
- Emergency preparedness and response procedures.
- Disposal of medical and other hazardous waste.

Training and Competency

- Policies and procedures relating to personnel education, training, and competency programs.

Information Technology (See Section I: Repository Information Management Systems)

- Procedures for validation and documentation of the information technology (IT) system including backup routines.
- *Audit* trail.
- Software bug tracking, troubleshooting/help desk functions, and resolution procedures.
- IT security and access policies and procedures.

D4.3. Quality Assurance

D4.3.1. Validation/Qualification

A validation process to ensure accuracy, reliability, and consistent intended performance should be employed prior to implementation of (and after changes to existing) instruments, reagents, labels, and processes employed in specimen collection, processing, storage, and retrieval.

D4.3.2. Key Performance Indicators (KPI)

Repository leadership should periodically review the overall effectiveness of their quality management system. For example, the identification of a specific set of performance metrics, tracked over time, may serve as an indicator of overall effectiveness of the quality management program. Such metrics could include:

- Percentage of correctly located specimens during quarterly inventory audit.
- Percentage of specimens received in the repository that are acceptable and/or appropriately labelled.
- Percentage of repository-shipped specimens received within the expected/acceptable temperature range.

In these examples, higher percentages are better, and repository leaders could set thresholds requiring corrective action (see Corrective and Preventive Actions, below). The selected KPIs can evolve over time.

D4.3.3. Non-Conformities

A process for documenting deviations from established policies and procedures should be established. A complete "incident reporting system" may be instituted whereby situations (*e.g.*, lost or damaged specimens, client complaints, adverse safety occurrences) are documented and investigated to:

- Facilitate "root cause analysis" for the event.
- Identify trends based on operational components (*i.e.*, failing equipment, bad *lots* of reagents or consumables, an inappropriate SOP).
- Prevent such episodes from reoccurring.

D4.3.4. Corrective and Preventive Actions

A process centered on development, implementation, and documentation of actions to correct an incident when it has already occurred (Corrective Action) or to avoid its occurrence before it has occurred (Preventive Action). These actions help leadership determine and implement the appropriate response to correct the initial undesirable situation.

Best Practice: Repositories should utilize a quality metric system as a way to measure the effectiveness of the quality assurance program and have plans to address deficiencies that may arise.

D5. RECORDS MANAGEMENT

Records (historical footprints) comprise information compiled as registered and recorded evidence that is permanent and traceable. Records maintained may include but are not limited to: training documents, *informed consent*

documentation, procurement records, processing records, assay reports, equipment maintenance records, *audit*/review reports, specimen storage location information, *material transfer agreements*, specimen distribution, *quality control* records, and all relevant forms. Records should be created and maintained in a manner that allows steps to be clearly traced and enable sample *chain of custody*. Security systems should be adequate to ensure the confidentiality and security of all stored records. Access to records should be on a "need to know" basis.

Best Practice: Repositories should develop a complete records management system to track all repository operations.

D5.1. Recordkeeping

A repository may develop a variety of template forms and spreadsheets to allow for effective recordkeeping. Uniform systems of documentation improve consistency in the tracking and monitoring of repository activities. Examples of forms include those to monitor equipment operations and repair, nonconformity or *incident* reports, and periodic equipment maintenance and calibration.

Forms should have a unique number and a distinct title and include the date that the version of the form was created (*i.e.,* version tracking). The forms should be easily accessible and saved in an electronic shared file system.

Best Practice: Forms or spreadsheets to record the most important pre-analytical data that may affect the quality of the biospecimens should be developed and maintained in the repository's records management system.

Best Practice: Forms should have a unique number and a distinct title and include the date that the version of the form was created (*i.e.,* version tracking).

D5.2. Record Corrections and/or Amendments

Corrections or amendments (changes) to a hard copy record should be made in ink with a single line drawn through the altered text. Corrections should be initialed and dated by the individual making the correction or amendment. Corrections in electronic records should be noted and tracked. Amendments tracked should include the name of the individual making the amendment, the time and date at which the amendment was made, and the reason for the amendment. Inventory systems that have the ability to maintain an audit trail are recommended.

Best Practice: Follow Good Documentation Practices as per the appropriate Quality Management System and regulatory requirements (*e.g.*, College of American Pathologists (CAP), Good Clinical Practice (GCP), Good Manufacturing Practice (GMP)). Dates should implement a format that is unambiguous and follows the country's conventions for designating dates (examples: ddmmyy or ddMonyyyy; where dd stands for day, mm or Mon stands for month, and yy or yyyy stand for year).

D5.3. Record Retention

Unless otherwise specified by contract, corporate or government policy, or other agreement, each repository should specify the length of time for retention of each type of record in its policies. Additionally, the repository's policy should indicate how records that are no longer needed should be destroyed or transferred. For example, a repository may archive equipment maintenance and repair records following the retirement of the equipment.

Retention of records for specimens or collections that are no longer active (*e.g.,* closed) or when samples have been destroyed or transferred from the repository may or may not require further retention, depending on the type of repository and its quality management system and policy requirements. In some instances, repositories may specify in their policies that information pertaining to collections that are inactive or specimens that have been removed from the repository should be retained in the repository *database* for tracking and documentation purposes.

For *natural history collections*, data and metadata (and to the extent known, all other data related to the use of the specimen) should be stored indefinitely, unless otherwise dictated by the agreements with the country of origin.

D5.4. Data Security

Data integrity as well as access control have to be considered. Electronic records should be backed up daily on a network or remote secure server. Data

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may or may not be sensitive and require protection. This may differ between data regarding human subjects (including under any data protection laws operating in the repository's country) and non-human specimens. In the latter case, data are generally regarded as less sensitive and may be open-access. In some cases, provider countries may require detailed distribution data of specimens be kept secure to minimize threats to endangered species.

A repository should develop a system for archiving records that are not currently needed for daily activities but need to be retained as described in Section D5.3. Record Retention. This system should allow all archived records to be accessible for audits and inspection as defined in Section D7. Internal Audits.

Best Practice: Arrangements should be made to store all critical records at a remote location, potentially with an off-site data security company.

Best Practice: Physical and electronic access to records and documents should be restricted and assigned based on roles; authorizations for access should be documented and available for audit.

Best Practice: Any physical documentation held onsite that contains sensitive information, (*e.g.*, confidential donor/client information such as Personally Identifiable Information [PII] or Institutional Animal Care and Use Committee [IACUC] sensitive information) should be locked in secure fire and water proof enclosures with controlled access.

Best Practice: When records are stored for prolonged periods or stored remotely, a periodic recall of a portion of the electronic data should be performed to verify the integrity of stored records. The frequency for performing this test should be defined in an SOP.

D5.5. Availability for Inspection

Records should be readily accessible for inspection by authorized personnel from regulatory agencies (these may vary for each country or state, depending on the regulatory agencies with jurisdiction over those activities) and Quality Assurance personnel. Access to privacy records or confidential client information should be restricted to limited repository staff members authorized to grant access to inspectors from regulatory agencies and other approved auditors.

D6. QUALITY STANDARDS

A variety of standards exist to allow for confidence and reproducibility in repository practices. While each of the standards described below can be implemented to support various repository activities, there are costs involved in the attainment of each standard and all the standards may not be appropriate for every repository.

D6.1. Good Practices

Good Practices (GP) are regulatory guidelines that should be interpreted by the repository to fit its particular circumstances. GP may be preclinical (Good Laboratory Practice [GLP]) or clinical (GCP) and GMP may be more relevant to industry repositories. Academic and other small repositories may wish to aim toward GP guidelines to instill confidence in the implementation of their SOPs. Generally, these standards are interpreted as follows:

- The facility is in a secure, locked area with limited access for unauthorized persons.
- Personnel should be trained in all procedures and successful completion of such training is documented with evidence of updates, if required, on a periodic basis.
- The facility is subject to internal QA audits and/or site visits by external clients and agencies, as appropriate. The agencies that audit vary by local, state, national/federal, or international regulations.
- Procedures are documented in SOPs that are approved by appropriate personnel and are changed or updated only under strict document control rules.
- Records are maintained with respect to the purchase of new equipment, maintenance, and repair activities, as well as equipment disposal. Examples of information tracked may include but are not limited to the name and model number for the equipment, name of manufacturer and contact information, serial number, date of acquisition, maintenance and repair, etc.
- Maintenance of records for critical materials and reagents used by the repository. Examples of information tracked may include but not be limited to: the item name, company from which the item was purchased, date of purchase, expiration date, and all related SDS.

- Deviation reports are produced for all events that fall outside SOPs.

D6.2. International Organization for Standardization

The International Organization for Standardization (ISO) is a worldwide federation of national standards with headquarters in Geneva, Switzerland. The organization was founded in 1946 to develop a common set of standards for manufacturing, trade, and communications organizations.

ISO/DIS 20387:2017(E) Biotechnology Biobanking General Requirements for Biobanking has been developed to enable biobanks to demonstrate operational competency and that they can provide biological resources (materials and data) of appropriate quality. It specifies general requirements including quality control requirements for the competence, impartiality, and consistent operation of biobanks to ensure appropriate quality of sample collections. This is a working document, foreseen to be published in 2018.

Additional relevant ISO standards:

- ***ISO9001:2015 Requirements of Quality Management Systems*** – a system standard, not a product standard. Its primary purpose is to provide organizations with useful internationally recognized models for operating a quality management system. Specifies requirements for a quality management system where an organization needs to demonstrate its ability to consistently provide products that meet customers' and applicable regulatory requirements.
- ***ISO/IEC 17025:2005 Quality Systems for Testing and Calibration Laboratories*** – provides general requirements for laboratories performing tests and/or calibrations, and sampling. ISO/IEC 17025 covers the use of standard methods, non-standard methods, and laboratory-developed methods. This standard incorporates key requirements of ISO9001:2015.
- ***ISO /IEC 15189:2007 Medical Laboratories*** – includes requirements for quality and competence, which are particular to medical laboratories.
- ***ISO 17034:2016 General Requirements for the Competence of Reference Material Producers*** – provides the general requirements that a reference material producer must demonstrate if they are to be recognized as competent to carry out the production of reference materials. References ISO/IEC 17025 as a normative document[1].

D6.3. Other Relevant Standards

Additional standards that may be applicable to repository operations include those established by the Clinical & Laboratory Standards Institute (CLSI), American Association of Blood Banks (AABB), and European Committee for Standardization (CEN, French: Comité Européen de Normalisation) (see Appendix A: Internet Resources).

Best Practice: The repository should implement multiple (or a combination of) quality standards to fit the type of services provided.

D7. INTERNAL AUDITS

Repositories should be subjected to regular audits. Audits cover the implementation of all SOPs that govern the repository. Audits may be done on a quarterly, semi-annual, or annual basis or in response to a non-compliance incident, accident, or a change/deviation in procedure required in the light of new information or alterations to ethical, regulatory, or health and safety issues. A designated individual familiar with the specific work being reviewed but not directly involved in that work should be responsible for each audit. For this function the individual should be someone who is not directly supervised by the Director (*e.g.,* they should report to a separate department or division responsible for quality assurance).

Regular audits for the inventory system should be performed and primarily directed at prevention of non-conformities as well as detection, corrective action, and process improvement implementation (see Section I2.1. Specimen Location).

Best Practices: The repository should have a procedure for periodic verification of the inventory and associated data. Random sampling from each storage unit using a predefined acceptable quality level can be used for QC purposes.

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D8. ACCREDITATION AND CERTIFICATION

D8.1. Accreditation

National accreditation bodies can accredit a repository to national or international accreditation standards.

D8.1.1. College of American Pathologists Biorepository Accreditation Program (BAP)

In 2012, the CAP introduced a BAP to closely parallel their accreditation process for clinical laboratories in North America. The CAP Biorepository Accreditation Program has a particular focus on Quality Management, as well as peer-to-peer dialogue aimed at improving Biorepository practices. Topics covered in the program include information technology, equipment/instrumentation, specimen handling and QC, quality management, personnel, safety, facilities, and regulatory requirements.

D8.2. Certification

Certification provides an official document attesting to a status or level of achievement. Certification to international standards, such as ISO9001:2015, or to national standards, such as NF S96-900, can be obtained by an independent body, which itself is accredited to ISO/CEI 17021 as a "certification body". Certification may also be obtained from non-accredited bodies (*i.e.*, Canadian Tissue Repository Network [CTRNet], NSW Biobank Certification Program) or by performing a self-assessment survey (Biobank Certification Program, Biobanking and BioMolecular Resources Research Infrastructure [BBMRI] self-assessment survey).

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SECTION E: METHOD VALIDATION AND QUALITY CONTROL CONSIDERATIONS

E1. VALIDATION OF SAMPLE PROCESSING METHODS

Repositories should use validated *processing* methods for their specimens. The *repository* can use scientific literature, feedback from the end users, and/or laboratory *quality control* results to evaluate and validate a processing method. The repository should list the circumstances requiring new validation measures to be taken (*e.g.*, instrument changes, specimen type changes). Each processing method should be validated for one or more specific intended end uses.

If no relevant scientific literature is available, the repository may have biospecimen research performed to assess the potential impact of the most important pre-analytical variables, following recommendations on biospecimen research. Features of biospecimen quality, including structure of proteins, function of enzymes, level of metabolites, gene expression levels, DNA methylation status, cell viability, and microorganism viability, can be affected by the specific procedures followed during *sample* collection, transport, isolation, and storage.

Pre-analytical variations should be noted whenever possible and appropriate as an important component to any QMS[1,2].

Examples of *in vivo* pre-analytical variations include:

- Patient's clinical condition
- Timing of collection
- Medication
- Organism's environmental niche/type of habitat, host, axenic state, season of collection, and microbial phase variation

Examples of *in vitro* pre-analytical variation elements include:

- Type of collection tube
- Pre-centrifugation delay and temperature
- ***Warm*** and ***cold ischemia*** times for solid tissues
- Method of sampling
- Type and duration of fixation
- Time delay before placing into long-term storage
- Type of long-term storage
- Exact protocol of cryopreservation and of restoration for environmental specimens

Implementation of a system to track pre-analytical variables will facilitate tracking and communication of the critical sample processing steps[3,4] in lieu of more sophisticated methods found in relational *databases* and laboratory information systems (LIS/LMS) that allow for aggregation of pre-analytical data (*i.e.*, time to processing, time to storage).

Best Practices: A pre-approved documented method evaluation plan should describe the methods used in the verification/validation, what is in/out of scope of the verification/validation, and the proposed criteria which will be used to determine the outcome of the evaluation. A summary *document* should be created after the validation exercise to accurately represent the results of the method validation.

Best Practice: External Quality Assurance programs should be followed, where available, at least once a year.

E2. METHOD EVALUATION CONSIDERATIONS FOR SPECIFIC TYPES OF SPECIMENS

Many of the QC processes are generic across all types of repositories and they concern the four "pillars" of *collection* quality:

- **Authenticity:** correctly assigned identity.
- **Purity:** freedom from contamination (when applicable).
- **Stability:** capability of a sample material to retain the initial value of a measured quantity for a defined period of time within specific limits when stored under defined conditions[5].
- **Consent:** for human specimens, sample type and usage is consistent with the level of consent provided by the participant.

Depending upon the molecular analyses that will be performed by the end-user, it may be advisable to extract and analyze matching molecular entities (*e.g.*, DNA, RNA, proteins) as a part of the biospecimen quality control testing[6,7,8].

QC measures for specific types of biospecimens can also be dictated by national/federal or international rules and regulations (*e.g.*, health and safety and bioethics)[9,10,11,12,13].

Best Practices: Consider creating a 'certificate of analyses' document for critical biomaterials (*e.g.*, cells). This document would contain the details needed to ensure consistency between lots and analysis methods used.

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E2.1. Quality Control Considerations for Specimens

E2.1.1. Quality Control Considerations for Solid Tissue Specimens

QC examination of tissues collected for research should be appropriate for the research protocol. QC of tissue ranges from microscopic examination of an *aliquot* that is representative of a specific tissue by a pathologist, cell biologist, or an equivalently trained individual to molecular quality control where nucleic acids and proteins are characterized. The highest quality control measures ("platinum" level) involve enriching the diseased population of tissue through macro- or micro-dissection of frozen or formalin-fixed, paraffin-embedded sections and also potentially performing molecular analyses. Platinum-based approaches are, however, costly and potentially exhaust specimen availability.

Best Practice: For "excess" tissue collected by the pathologist from diagnostic surgical resection specimens, verification of the diagnosis and percentages of tumor and necrosis should be performed for each aliquot due to tissue heterogeneity. This can occur via pathologist top-slide analysis for embedded aliquots or via mirror-slide analysis to permit snap-freezing of aliquots without embedding medium.

Best Practice: Tissue quality is fundamentally tied to processing conditions (*e.g.*, ischemia times, time to processing, fixation type/duration, time to storage) which may impact downstream applications and should be closely monitored and recorded as part of the quality management program.

E2.1.2. Quality Control Considerations by Virtual Microscopy/Digital Pathology

E2.1.2.1. Virtual Microscopy

Virtual microscopy is the method of producing a digital image of a tissue section or cytological preparation mounted on a glass microscope slide that is suitable for visual examination, *annotation* of regions of interest, and interpretation. This method uses scanning equipment at a range of magnifications to produce digital images suitable for remote web-based viewing and archiving. These digitized images can approximate the process of viewing slides microscopically, including the capacity to adjust viewing magnification and focus on specific regions of the image. When optimized, image quality may be sufficient quality control to confirm the histopathological diagnosis and composition of banked research specimens.

The use of this technology in certain situations may provide advantages compared with microscopic examination of slides, including: elimination of shipping glass slides, facilitating rapid review, reducing costs of tracking and replacing lost or broken glass slides, and allowing accessibility anytime via the Internet as well as allowing concurrent review of the same slide image by multiple viewers[14]. Depending upon the availability and type of imaging systems, at some locations it may be more cost effective to provide a tissue section on a glass slide to investigators. Also, high-quality images require optimal scanning and significant data storage capabilities; thus the storage capacity required for a large number of such images must be taken into consideration and only the most "diagnostically difficult" cases may necessitate digital storage.

E2.1.2.2. Digital Pathology

Digital pathology, built around the examination of digital virtual microscope images, is a workspace environment which integrates with other electronic applications such as laboratory information systems, electronic medical records, medical imaging, molecular testing systems, and specimen tracking systems. Digital pathology also allows complex image analysis of both morphology and tissue-based assays (*i.e.,* immunohistochemistry, immunofluorescence) and can allow simultaneous viewing of multiple different images concurrently.

Image analysis of specimens could ultimately be used to automate quality control in tissue banks by augmenting or replacing the traditional morphologic review of actual tissue sections. It could aid in assessing tissue quality by detecting and measuring features

such as % tumor, % stroma, % necrosis, % cellularity, and other morphologic features. Such approaches require validation prior to implementation.

E2.1.3. Quality Control Considerations for Fluid Specimens

Different collection, processing, and storage procedures may adversely affect the structure and/or function of molecular components in fluid biospecimens (*e.g.*, serum, plasma, urine, saliva, cerebrospinal fluid). In some situations, fluid biospecimens may require assessment as to their integrity in view of the detection or measurement of specific *analytes*. Molecular markers to assess specific pre-analytical variables can be used, such as the hemoglobin content to assess hemolysis or the sCD40L content to assess exposure to room temperature[15]. In many instances, quality control can only be performed in reference samples and in a targeted manner once the end-use analysis is known.

E2.1.4. Quality Control Considerations for Cell Specimens

Contamination control methods for eubacteria, fungi, mycoplasma, and viruses can be applied to primary cell cultures or cell lines. DNA fingerprinting methods can be applied for identification of established cell lines. Testing for downstream utility can include functional assays of the cell specimen (*e.g.*, ELISpot, cell proliferation). Cell viability and/or purity of the cell suspensions can be assessed after thawing of a representative frozen aliquot.

E2.1.4.1. Assessment of Cell Viability

Estimation of the total number of recovered cells and of the number of viable cells in sorted or unsorted cell preparations from blood, bone-marrow, or other specimens are important for several research applications, including stem cell research. Cell number may be determined by several methods, including dye exclusion (*i.e.*, Trypan Blue) and vital staining using tetrazolium salts or fluorescent dyes such as fluorescein diacetate. It is essential to standardize viability assays and where possible back them up with unequivocal tests of functionality and clear evidence of cell division and growth. Determination of total and viable cells recovered post-thawing should be assessed both prior to freezing and at the time of thawing/warming to estimate loss due to freezing.

The phenomena of delayed onset cell death may impact evaluations of viability immediately post-thaw as compared to actual long term cell survival and functionality. For this reason, post-thaw assessment of cell viability may need to be expanded beyond a singular assessment via Trypan Blue (or similar assays) immediately post-thaw or after re-warming in the case of vitrified samples. An expanded assessment of post-thaw recovery (this may be referred to as True Yield/Viability) may include multiple methods of assessment including Live/Dead assays, cell death mechanism assays such as Annexin/PI, or metabolic assays such as alamarBlue or MTT, cell function assays (dependent on cell type), and assessment at multiple time points post-thaw/re-warming, especially within the timeline of delayed onset cell death. These expended viability and functionality assays may need to be balanced against the research uses of cells that are difficult to obtain and have limited supply.

E2.2. Quality Control Considerations for Microorganisms

Phenotypic characterization includes both macroscopic and microscopic morphology assessment. Genotyping (*e.g.*, DNA sequencing, polymerase chain reaction [PCR]-based profiling, microarrays), ribotyping, classical biochemical tests, and/or serotyping methods can be applied for taxonomical identification purposes. Functional assays include viability assays or assays for cytopathic effects.

Quality Control for purity can be performed; however, certain cultures need to be maintained in a non-*axenic state* (*e.g.*, obligate plant pathogens and assemblages of microorganisms, symbiotic and beneficial associates found in microalgae and cyanobacterial collections).

The World Federation for Culture Collections (WFCC) is a multidisciplinary commission of the International Union of Biological Sciences and

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a Federation within the International Union of Microbiological Societies concerned with the collection, authentication, maintenance, and *distribution* of cultures of microorganisms and cultured cells. Its aim is to promote and support the establishment of culture collections and related services and develop an international database on culture resources worldwide (see Appendix A: Internet Resources).

E2.3. Quality Control Considerations for Plant Specimens

The overarching QC process of plant biorepositories (*i.e.*, gene banks, culture collections, germplasm repositories, seed and field banks) ideally involves germplasm characterization before and after storage and at the point of dissemination as well as plant health (phytosanitary) checks, safety duplication, and passport documentation with assignment of an accession number.

In the case of seed materials, the International Seed Testing Organization has the mission to develop and publish standard procedures in the field of seed testing and encourage and establish uniformity in seed testing world-wide.

For clonally propagated plants (and other non-seed genetic resources such as pollen and dormant buds), quality testing includes assessment of viability, phytosanitary status, and disease management (comprising quarantine, disease indexing, and eradication).

Phenotype and genotype authentication can be a regulatory requirement for some crops and commercial forestry species and can include formal confirmation of certification status (trueness-to-type) by field-testing plants that are evaluated using specific phenotypic descriptors and as appropriate confirmation using molecular markers.

The detection, expression, and stability of genetically modified materials may be necessary. The risk assessment and management of transgene contamination is a requirement for certain types of collections.

Post-storage QC measures include assessments of viability, *morphogenetic competence*, *totipotency*, regeneration, biochemical stability (*e.g.*, for secondary product producing cell lines), phenotypic and genotypic stability (*e.g.*, characterization of somaclonal variation), and trueness-to-type assessment under field or glasshouse conditions using descriptors.

E2.4. Quality Control Considerations for Nucleic Acid Specimens

DNA and RNA can be assessed for integrity and fragmentation (*e.g.*, molecular weight, DNA Integrity Number, RNA Integrity Number), quantity/concentration, and purity. In addition, DNA can be assessed for the absence of cross-linking, human vs. non-human composition, the absence of PCR inhibitors, and the percentage of double-stranded DNA. RNA can be assessed for ratio of 5′ to 3′ amplicons (ΔCt), amenability to reverse transcription, and the maximum length of the quantitative real-time PCR (qRT-PCR) products.

E3. VALIDATION OF QUALITY CONTROL METHODS

Each QC method should be assessed by the repository or by the external laboratory performing the assays, for its accuracy, precision, limit of detection, and linearity (if applicable). External quality assurance programs using Reference Materials should be followed, when available, at least once a year[16,17].

Best Practice: Performance of assays should be trended to discriminate out of specification (out of trend) results. These results should be documented and reconciled where appropriate.

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SECTION F: SAFETY

F1. GENERAL

Issues related to safe operation of a *repository* are complex and depend on its particular activities. Regulations governing *safety* may be covered by national/federal, regional, or local regulations. Each repository should determine which areas of safety are applicable and develop an appropriate safety plan to protect its employees and visitors[1,2,3,4].

Safety plans are used to prevent or to minimize injuries to employees and visitors. In order to develop an effective safety plan, the likelihood and source of potential injuries for each employee should be identified. These will depend upon the *procedures* and activities that the employee performs as well as rooms in which they are likely to spend time[3,4]. Each employee and his or her supervisor should work together with workplace health and safety experts to identify potential sources of injury and reduce the risk of injury via changes in procedures or engineering. For example, this could include the use of safety equipment or the improvement of ventilation within a specific area[1,2,3,4].

Best Practice: Risk assessment should be carried out to ensure that all regulations are followed.

F2. NATIONAL/FEDERAL, REGIONAL, AND LOCAL REGULATIONS

Repositories should ensure they have reviewed and comply with national/federal, regional, and local regulations regarding the health and safety of employees.

F3. SAFETY INFRASTRUCTURE

The Director or other individual with overall responsibility for the organization has primary legal responsibility for the safe operation of all components of the organization including a repository; however, the day-to-day responsibility for safety is frequently designated to another individual and/or to a Safety Committee. While this person or group may be primarily responsible, the responsibility for safe operation also lies with each employee.

The organization in which a repository resides usually establishes a Safety Committee that is responsible for the overall safety plan of the institution, including periodic monitoring and updating. The Safety Committee usually appoints a Safety Officer to administer the program.

The Safety Officer establishes a safety training program and monitors and maintains compliance with the program, evaluates *incidents* and injuries, and recommends changes to the Safety Committee, as needed. The Safety Officer works closely with area supervisors to ensure adherence to all safety regulations[2,3,4].

F4. TRAINING

Employees should be advised of the potential hazards associated with working with *specimens* and sign an agreement to handle all specimens with the necessary safety methods. Individuals should be trained to follow universal precautions, *i.e.* to handle all specimens as though they are potentially hazardous, and should take appropriate precautionary measures. Additional risks may be present when staff come into contact with patients during the consenting process (*e.g.,* HIV or tuberculosis) or during *collection* of non-human specimens (*e.g.,* zoonotic pathogens that are transmissible from animals to humans). Repositories receiving environmental *samples* should provide training to minimize exposure to toxic substances See Section G: Training for a full discussion of training issues.

F5. PERSONAL PROTECTIVE EQUIPMENT

All persons, including visitors, should wear appropriate clothing (*i.e.,* lab coats, long pants, and covered shoes; not shorts, skirts, or open-toed shoes) as well as eye protection, depending on exposure. Appropriate gloves are recommended for handling any specimens, chemicals, or hot or cold equipment and supplies. If exposure to hazardous materials occurs, hands and other exposed areas of skin should be washed. Laboratory coats may be laundered or disposed; this choice depends upon the type and extent of exposure.

Eyes and other mucous membranes must be protected from exposure to *biohazardous* materials and chemicals. Depending on the likelihood of exposure, this protection may be accomplished via goggles, safety glasses, or face shields. These should be worn any time there is a likelihood of exposure.

Respiratory protection against chemicals is only necessary when the exposure to vapors of toxic chemicals exceeds the standard specified by regulatory agencies. If respirators are required, they must be individually fitted.

Appropriate safety equipment for specific tasks must be utilized by all staff as designated in the repository's SOPs.

F6. SAFETY TOPICS

F6.1. Biological Risk Assessment and Safety

All human specimens (and to a lesser extent animal specimens) whether fixed, paraffin-embedded, fresh frozen or *freeze-dried* should be considered as potential biohazards. As the extent of alteration of tissue increases (*e.g.,* fresh to frozen to fixed to paraffin-embedded), the risk from various infective agents is usually reduced[3,4]. However, certain agents such as prions (*e.g.,* the causative agent for Creutzfeldt-Jakob disease ["mad cow disease"], scrapie, deer/elk wasting disease, other transmissible spongiform encephalopathies) may still be infective even when tissues are fixed and processed to paraffin blocks or autoclaved. Prions are very difficult to inactivate and cannot be destroyed by ethyl alcohol, bleach, detergents, or other *disinfectants*. Consequently, all human and animal specimens independent of their state should be handled at Biosafety Level 2 or higher, *i.e.,* should be handled as if infected with agents that may be pathogenic to humans. Individuals should receive training so that they can recognize symptoms that accompany the exposure to certain harmful compounds and diseases to which staff are exposed[5] and reduce their risk as much as possible.

Disinfectants should be chosen according to repository or institutional preference. Further information on disinfectants may be obtained from the Centers for Disease Control and Prevention. Repositories should develop a Bloodborne Pathogen Exposure Control Plan or similar to eliminate or minimize occupational exposure to bloodborne pathogens. The plan should include a determination of employee exposure, methods to control exposure (*e.g.*, universal precautions, personal protective equipment, engineering controls), appropriate vaccinations, post-exposure evaluation and follow-up, communication of hazards, and accurate recordkeeping. Applicable regulations covering occupational exposure to bloodborne pathogens should be determined.

Staff can consult *biosafety* manuals on the properties of human pathogens and recommendations for laboratory work involving these agents (see Appendix A: Internet Resources).

Best Practice: Staff at risk of exposure to vaccine-preventable infectious diseases should undertake appropriate immunizations.

F6.1.1. Biological Hygiene Plan

Biological hygiene plans should include the following:

- Approaches to prevent, contain, and clean up biological spills. The plan should include a description of how to dispose of waste and biologically-contaminated materials resulting from the clean-up.
- Approaches to the safe, lawful, and appropriate disposal of all repository materials that are no longer deemed necessary.
- Approaches to ventilation failure, evacuation, medical care, and reporting of biological exposure incidents.
- A description of areas where eating, drinking, storing food and beverages, smoking, gum chewing, and application of cosmetics are not permitted. This should include areas where specimens are processed, stored, and handled.
- Requirements for the use of a *Biological Safety Cabinet* to reduce the risk of exposure to potentially infectious disease.
- Requirements to minimize the generation of and exposure to aerosols.

F6.2. Chemical Safety

Many countries have developed regulations that govern activities relating to chemical safety that may affect repositories (see Appendix A: Internet Resources). These laws may mandate that an organization develop a written chemical hygiene plan. The chemical hygiene plan should be capable of protecting employees from hazardous chemicals in the laboratory and of keeping chemical exposures below the action level (or in its absence the Permissible Exposure Limit).

All chemicals used in repositories should be labeled, stored, and disposed of appropriately. They should also have MSDS or SDS available for easy reference for employees who will potentially come into contact with the chemicals and auditors who will look for these *documents*. SDS are available from manufacturers and should be provided either in hard-copy or from a provided URL for downloading.

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Best Practice: Replace chemicals that are hazardous to staff or the environment with alternatives when possible.

F6.2.1. Chemical Hygiene Plan

Chemical hygiene plans should include the following[2,3,4]:

- Approaches to prevent, contain, and clean up chemical spills. The plan should include a description of how waste and other chemically contaminated materials resulting from the clean-up are to be disposed of.
- Approaches to the safe, lawful, and appropriate disposal of all repository materials that are no longer deemed necessary.
- Approaches to ventilation failure, evacuation, medical care, reporting of chemical exposure incidents, and chemical safety drills.
- A description of areas where eating, drinking, storing food and beverages, smoking, gum chewing, and application of cosmetics are not permitted. This should include areas where specimens are processed, stored, handled, or where chemicals are used.
- Guidance on allowable pipetting methods (*e.g.,* mouth pipetting and mouth suctioning for starting a siphon should be prohibited).
- Guidance on the appropriate use of all chemicals used in the fixation or *processing* of tissues.
- Requirements for the use of chemical fume hoods to minimize exposure to vapors from hazardous chemicals (*e.g.,* formaldehyde or xylene).

Best Practice: All regulations should be followed as to chemical safety.

F6.2.2. Compressed Gases

Compressed gases such as Argon present a risk of asphyxiation by displacing oxygen. While eye protection is not required for working with compressed gases, it is recommended. Employees should wear oxygen monitors while handling compressed gas cylinders or working with compressed gases. Cylinders should be stored in well-ventilated areas in compliance with appropriate regulations. Free-standing cylinders should be secured to the wall to prevent tipping.

Best Practice: Appropriate protective equipment should be utilized when working with compressed gases.

Best Practice: Crush-resistant safety shoes (*e.g.,* steel-toed) should be used when moving heavy tanks or transporting cylinders with floor trucks.

Best Practice: Compressed gases should be stored and transported in well-ventilated areas, with detectors and alarms fitted.

F6.3. Electrical Safety

Equipment should be tested for grounding when first purchased and yearly thereafter, except in specific circumstances such as devices that are protected by double insulation. All electrical base plugs should be in good condition. Electrical work should be done with great care ensuring that personnel in the affected work area are protected during the removal of fuses and while working near a water source. There should also be written warnings regarding the danger of electrocution at the fuse box. Electrical equipment should be unplugged prior to service, as appropriate, and staff should have visible control of the plug to avoid inadvertent energizing of the unit.

Mechanical storage units are rated to function at a specific voltage. Buck boosters will activate to stabilize the voltage should the level drop below that specified. If conditions persist, they can result in overheating of the wiring or components and possible failure or fire. Routine checks of facility voltages and/or noting of prolonged use of the buck boosters will alert staff to low-voltage conditions.

Best Practice: All new electrical equipment should have an electrical inspection prior to installation to ensure proper electrical supply and usage.

Best Practice: Surge protectors or voltage regulators are recommended for stand-alone freezers if this is not part of the building electrical infrastructure.

Best Practice: All electrical equipment and base plugs should be tested for grounding.

F6.4. Fire Safety

The local fire department or the organization's Safety Officer can inspect a repository to evaluate fire safety prevention plans. Prior to such inspections and on a regular basis (*e.g.*, annually), fire drills should be conducted and fire suppression equipment and safety showers/eye wash units should be tested. Emergency pathways should be posted at all room exits. Emergency exits should never be blocked, obstructed, or locked and hallways should not be obstructed or cluttered. Flammable agents should be stored appropriately, including the storage of large amounts of flammable agents in fire cabinets. Refrigerators/freezers that represent reduced dangers of causing combustion can be purchased for use in research laboratories. Smoking, if permitted at all, should be limited to designated external areas. Furniture, rugs, and equipment should be constructed of non-flammable material. Regulations for types of doors to serve as fire barriers should be followed as should fire requirements for construction of buildings that house specific activities (*e.g.,* laboratories). Fire safety will be governed by national/federal, regional, and local requirements (see Appendix A: Internet Resources) For additional information on fire prevention systems see Section B7.

Best Practice: Fire safety should be an important component of an organization's safety plan.

F6.5. Physical Safety

The physical safety of employees should be considered in all repositories. Physical safety ranges from preventing falls to ensuring that employees are not physically injured by other means. Ensuring physical safety involves careful maintenance of the physical plant and facilities, such as handling and/or prevention of tears in rugs and fixing broken steps. Care should be taken to ensure that water, soap, paraffin, and other substances do not create a slippery surface on floors. Power cords should be appropriately covered and inappropriate use of ladders or use of chairs as ladders should be prohibited to prevent falls. Similarly, unsecured gas cylinders, unbalanced file cabinets, large bottles containing liquid, and inadequately secured shelves can all lead to injuries via falling or moving agents or structures.

Also included in causes of physical injuries are repetitive-motion injuries (*e.g.,* pipetting) and back injuries resulting from movement and inappropriate lifting. Repository staff members may be required to stand on step-stools and lift heavy racks vertically out of the freezer in order to access specimens. Back injuries can be avoided by installing an automatic pulley mechanism to aid in the removal of the racks from the freezers. By analyzing an employee's work environment and improving the placement of objects and providing the proper tools, the potential for injury will be greatly reduced. When *ergonomics* is applied correctly in the work environment, visual and musculoskeletal discomfort and fatigue are significantly reduced. Where feasible, repositories may consider automated specimen input and *retrieval* systems to reduce physical strain on technical staff. Ergonomics should be considered when developing a repository or organizational safety plan. Physical injuries that are difficult to avoid include minor cuts (*e.g.,* paper), bumps, and strains due to inattentive actions. However, such minor injuries should not be compounded by exposure to biohazards or chemical hazards. The overall safety program should address other hazards that can be prevented or ameliorated by wearing proper protective equipment and clothing such as the use of gloves to avoid thermal burns from both heat and cold (*e.g.,* dry ice, liquid nitrogen). Check the occupational safety laws of your region (see Appendix A: Internet Resources). Repositories should maintain a first aid kit for use by repository staff and visitors, if required.

For equipment that may be located within a confined space (*e.g.,* large robotic stores for DNA samples), procedures should be developed to assure that the equipment is not moved or operated during routine cleaning, maintenance, or repair.

Best Practice: Physical safety and ergonomic considerations should be included in an organization's safety plan.

F6.6. Radiological Safety

While few repositories will store or use radioactive material, those that do need a radiological safety plan. Specific training is required for personnel who use or come into contact with radioactive material as well as in the use of specific radiation monitoring equipment. Work with radioactive materials in many countries requires a license. Repository staff

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should refer to the appropriate guidelines for the country or region in which the repository is located.

Best Practice: A designated staff member should be responsible for ordering, storage, documentation of distribution/use of the radioactive product, and ensuring that isotope limits are adhered to.

F6.7. Dry Ice Safety

Those working with *dry ice* in the laboratory should use appropriate protective wear approved for low temperatures to avoid skin damage. Dry ice sublimates into large quantities of carbon dioxide gas which could displace oxygen and pose a danger of asphyxiation.

IATA packing instruction 904 (IATA PI 904) requires that dry ice be labeled specifically with a diamond-shaped black-and-white label with the UN 1845 designation. Arrangements must be in place to ensure adequate ventilation so that pressure build-up does not rupture the packaging (see Appendix A: Internet Resources). Further information on dry ice is provided in Section J: Packaging and Shipping.

F6.8. Liquid Nitrogen Safety

Those working with or around liquid nitrogen (LN_2) and other cryogenics should use appropriate protective wear and *document* their appropriate training. A full face shield should be used to protect the eyes and face from splashes when working with large volumes of LN_2. Non-absorbent, insulated gloves (cryogenic gloves) should be worn when handling anything that is or has been in recent contact with LN_2. Cryogenic gloves are made to be used only in the vapor phase of LN_2 and should not be immersed in the liquid itself. A long-sleeved, buttoned lab coat should be worn at all times when working with LN_2 to protect the body. Non-absorbent cryogenic aprons can also be used and should be used when splashes may occur. Clothing with open pockets and turn-ups where liquid may collect should be avoided. Shoes should cover the entire foot and be sturdy and non-absorbent when working with LN_2. Nitrogen is odorless, colorless, and tasteless. As LN_2 evaporates it will reduce the oxygen concentration in the air and cause a potential risk of asphyxiation, especially in confined spaces and may necessitate the use of O_2 monitoring devices (see Section C2.5.1. Oxygen Sensors).

Best Practice: All individuals working in areas where LN_2 is being utilized (including non-repository staff) should be made aware of potential hazards and trained in appropriate safety policies. Signs should be posted indicating the use of proper protective gear and need to follow established safety procedures.

Best Practice: Appropriate safety PPE should be used when dealing with liquid nitrogen.

Best Practice: O_2 monitoring should be installed in any areas of the facility where LN_2 is utilized.

F6.9. Carbon Dioxide Safety

Carbon dioxide (CO_2) gas is a colorless, odorless, non-flammable gas. In addition to presenting a risk of asphyxiation by displacing oxygen, carbon dioxide is a toxic gas that can present exposure risks such as changes in blood pressure, tinnitus, headache, irregular heartbeat, difficulty breathing, etc. While eye protection is not required for working with CO_2 gas, it is recommended. Employees should wear oxygen monitors while handling CO_2 cylinders or working with CO_2 gas. Cylinders should be stored in well-ventilated areas in compliance with appropriate regulations. Free-standing cylinders should be secured to the wall to prevent tipping.

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SECTION G: TRAINING

G1. GENERAL

All *repository* staff should be adequately trained to perform the tasks required by their particular position description. Proper training is important to ensure quality in *specimen* handling. In some areas of *safety*, adequate training may be mandated by national/federal regulations and severe penalties may be imposed on the repository and repository personnel if training is not provided as required.

Support for training is essential for adequate implementation of certain tasks and in some cases might require additional resources or time away from regular responsibilities.

G2. TRAINING INFRASTRUCTURE

G2.1. Training Program

Every individual who enters the repository for the purpose of performing work should be trained in the particular functions or tasks which they are asked to complete. Training should be task and location specific and be designed for the particular position that is expected to carry out the work. Training should involve instruction in the use of any equipment used and involve appropriate *quality control* and *quality assurance* practices. See Section D: Quality Management for a full discussion of quality control and quality management issues.

Training for some functions may be provided by departments outside of the repository (*e.g.,* maintenance staff, equipment vendors, infection control, professional air transport regulatory trainers); however, repository staff should ensure that all individuals who enter the repository follow required safety and other procedures in performing their particular tasks. Training must be in a language the employee understands and the level of training must be appropriate to the employee's level of comprehension.

Academic or other institutional training, in the form of courses, may be available from some institutions. The syllabus of such courses should be reviewed for correspondence with particular specific training needs and decisions made accordingly. Examples of areas covered by such courses may include legal aspects, management and financial aspects, cellular and molecular biology, statistical aspects, or quality assurance.

Repository staff should be asked to review any written *procedures* for which they are responsible prior to the commencement of their "hands-on" training. A written record indicating that the employee has read the pertinent procedures should be kept in the employee's training file (see Section G2.7. Training Records). This record should include the title of the procedure, the employee's initials, and the date upon which the procedure was read. It is preferable that a short test be administered to personnel concerning the material that is presented for the employee's review.

At a minimum, it is recommended that repository staff be trained in the following areas:

- Facility security and procedures, including emergency response.
- Workplace health and safety.
- Technical procedures, including handling of all materials in the repository.
- Management of records and *databases*.
- The ethical issues surrounding biospecimen research, as applicable.
- Regulatory requirements.
- Participant privacy and confidentiality.
- Material release, including *samples* and information.
- Good Practices (GLP, GCP, GMP), as applicable.

Best Practice: To ensure quality of repository activities, employee performance should be routinely monitored to identify needs for additional training between regular training intervals. Staff should be informed when first hired that routine monitoring of employees' performance is a part of regular practices for ensuring quality and is applicable to all repository staff.

G2.2. Trainers

The trainer is an employee who regularly performs the procedures in question, has completed the training program previously, and is skilled in explaining the elements of the task. The trainer is responsible for ensuring that the trainee understands each procedure and task. For special areas of training (*e.g.,* human subjects protection, privacy, safety), personnel with special expertise

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may provide the training. Experts via audio-visual methods including web-based technologies may also provide training. This approach may permit employees to complete special areas of training at their own pace when time can be scheduled based on the employee's daily activities.

During the training period, the trainer demonstrates, explains, and reviews the standards to be followed in conducting the procedure(s). The trainer should provide appropriate feedback, as necessary, on the trainee's performance of the procedure. The trainer should supervise the trainee in all tasks contained in the procedure(s) until the training phase has been completed. The training phase should not be completed until the trainer and trainee are both comfortable that the trainee is able to conduct the procedure without supervision.

Best Practice: After the training has been completed, the trainer should be available to answer questions when the task is being performed by the trainee for the first few times.

G2.3. Training Coordinator

The Director should ensure all aspects of staff training are covered and that SOP changes are communicated appropriately. The Director may delegate tasks to other repository members, who may operate as a Training Coordinator. The Training Coordinator may maintain the SOP manual and coordinate with the trainer responsible for that particular procedure when any revisions are needed either due to the expiration of the SOP or for technical reasons. The Training Coordinator closely coordinates issues related to training in safety with the organization's Safety Officer and with other individuals responsible for specific areas of repository procedures (*e.g.*, shipping and handling). The trainer also needs to have regular training to ensure their competency.

The Training Coordinator is responsible for monitoring, training, and maintaining appropriate training documentation of all employees. The Training Coordinator maintains records of employees to be trained in each required area, tracks the time of their periodic updates of training, informs the employees of potential times of training, and ensures the training is completed according to the required timeframe.

The Training Coordinator closely coordinates documentation of training and educational activities with personnel who maintain employee records, as needed.

G2.4. Frequency of Training

Training and repeat training should be conducted in accordance with applicable regulations and also in accordance with the needs of the particular tasks and positions held by repository staff. In many countries, regulations require training before the employee begins working and yearly thereafter (*e.g., biohazard* and chemical hazard training). Training for regular repository tasks should be implemented before staff are asked to perform those particular tasks. Repeat training should be performed according to a defined schedule described by SOPs. Supplemental training (sometimes in conjunction with "corrective actions" or a protocol change) may be required following the evaluation of particular *incidents* in order to prevent their recurrence or to enhance staff performance (see Section D4.3.4. Corrective and Preventive Actions).

Best Practice: Training should be periodic and documented and in accordance with the needs of the particular tasks to be performed.

G2.5. Cross-Training

Repositories should cross train personnel in a variety of procedures to alleviate staff burn-out, reduce turn over, and to maintain coverage should staff levels change.

G2.6. Training Documentation

Once the training is complete, a written record of the completed training should be made that includes the trainee's signature as well as the trainer's signature. Electronic signatures should be used for documentation of any electronic training that is received.

G2.7. Training Records

A training file should be maintained for each repository staff member and should include, but may not be limited to, the following:

- Position description that includes the job title and responsibilities, as well as the educational and work experience required to perform the specified task.
- Curriculum Vitae.
- Example of the employee's signature and initials.
- Copies of any certificates documenting that the employee has had specialized training. This should include training in shipping, safety, and applicable regulations such as those required in the country in which the repository is located (see Appendix A: Internet Resources).
- Documentation that an employee has read and understands all SOPs pertinent to the employee's responsibilities.
- Orientation to the repository.
- Documentation of analytical results to demonstrate proficiency in specified technical tasks. This should include results of reproducibility and/or quality control results.

The training file should be kept in the repository and be available for Quality Assurance or client review. The training file should be archived according to the repository's SOPs after the employee is separated from the organization. If an employee moves from the repository to another department within the organization, the employee's training file should be transferred to the new department. Further information on management of training records can be found in Section D5. Records Management.

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SECTION H: COST MANAGEMENT

H1. GENERAL

The *repository*'s activities should be detailed within a comprehensive business plan (see Section A3. Repository Development) which includes financial support to enable proper function. The business plan should be reviewed at routine intervals and as necessary to account for changes in governance, organizational structure, labor, materials, supplies, etc. Repositories should review and *document* costs related to personnel, labor, materials and supplies, equipment, equipment support, facilities, and qualification. An equipment replacement plan should be implemented and reviewed regularly to determine the actual costs of equipment, determine if repair and maintenance versus the cost of acquiring new equipment may be less expensive, be more efficient, and operate with fewer repairs. It is only when these costs are known that accurate budgets can be prepared and funding sources can be identified. Failure to accurately document costs may lead to unsustainable repository operations.

Requirements for financial support may vary depending on the type of institution with which the repository is affiliated. Considerations may include the repository's receipt of public or private funding and the amount of funding the repository must recover. To ensure continued operations without compromising quality, specific plans should be developed for five years and beyond to estimate long-term costs and revenues.

Best Practice: Repositories should develop a business plan based on objectives and strategy as well as known and estimated costs while ensuring that all costs are documented to support sustainability strategies.

Best Practice: Repositories should have long-term projections for sustainability in addition to annual budget plans.

H2. IDENTIFYING AND DEFINING COSTS

Developing an accurate assessment of costs required to support a repository can be complex and dependent upon potentially overlapping functions undertaken in the repository setting. Understanding operational costs is a key component of a repository business plan. Tools exist globally to identify the specific cost burden of repository operations and opportunities for revenue (see Appendix A: Internet Resources). Cost assessment development should include financial management representatives of the organization(s) with which the repository is involved, and, possibly, repository funders. Cost information for facilities, equipment, and labor may be available from current and historical records. Where possible, information should be obtained from within the organization or facility to determine current rates for overhead or indirect costs, personnel costs, facility costs (*e.g.*, costs for space, HVAC, utilities, labor), equipment depreciation, and maintenance to permit the development of a cost recovery plan. Terms and conditions of shared costs should be detailed in the business plan. Some repositories may, for example, have part of their operating costs covered by medical facilities or universities with which they are associated, or to which they provide service.

Critical costs for effectively initiating, developing, and maintaining a repository should be considered. The actual costs to be considered will depend on the function of the repository. For example, costs should be assessed for the following:

- Physical facilities (*e.g.*, lease, electricity, water, overhead).
- Staffing and administrative costs (*e.g.*, payroll including overtime, benefits, contract support, consultant fees, IT services).
- Specimen processing and storage equipment (*e.g.*, freezers, cabinets, liquid handling machinery, cryostats, nucleic acid extractors), and periodic *calibration* by vendors.
- Inventory management software, licenses, and maintenance.
- Consumables, operating supplies and gases (*e.g.*, buffers, reagents, chemicals, disposables, *disinfectants*, laboratory *safety* supplies, personal protective wear, liquid nitrogen, diesel).
- Minor equipment (*e.g.*, monitoring equipment, barcode scanners, computers, office equipment, telecommunications).
- Service contracts for equipment maintenance and disaster recovery.
- Possible certification and/or accreditation fees or other Quality Management fees.
- *Culling* and/or transferring *collections*.

Evaluation of all costs related to work streams, systems, equipment, and supplies should be completed prior to establishing fee schedules. Under some circumstances, for example, costs for collection should be included whereas

in others, only the costs for receiving and storing *specimens* should be considered. Likewise, costs for specimen testing may or may not need to be considered depending on the mission of the repository. The cost of specimen *distribution* should be calculated (*e.g.*, labor for pulling and inventorying specimens, shipping supplies, courier fees).

Once all costs are defined, it is important to review work processes and to consider the ability to optimize work-flow to improve cost recovery. Equipment and space should be multi-purposed whenever possible (*i.e.*, shared facilities). A variety of options may be available for reduction of labor costs while still performing the work of the repository with high precision and quality. Routine repository activities should be examined to determine if automation might be incorporated to more rapidly process, store, and/or retrieve specimens with accuracy and efficiency. While automation typically requires an increased initial expenditure, the result may be a reduction in labor and facility costs over time.

Best Practice: Prior to cost assessment, evaluate all work streams, systems, equipment, supplies, and services to enable cost recovery and to minimize waste.

Best Practice: The operational life of infrastructure should be considered in preparation for timely replacement and expansion purchases.

H3. COST RECOVERY

External funding may be obtained through grants, contracts, other private funding mechanisms, and user fees to cover the partial or full cost of collecting, maintaining, and distributing specimens. Even repositories that have most of their costs covered may wish to consider a nominal service fee to promote good stewardship and judicious use of resources. Regardless of funding sources, repository managers should prepare accurate, annual budgets to support orderly repository activities. Services and products should be provided according to quote-based, term-limited agreements.

Cost recovery policies should be developed with key stakeholders of the repository, potential recipients of the collected specimens, and, where appropriate, with study participant advocates. These policies should be reviewed regularly and adjusted as needed. Service fees should be kept within a range that accommodates cost recovery and permits maximum use of the repository. Additional policies should be developed to address the timely collection and non-payment of fees, as well as culling or redistribution of specimen collections that are no longer supported by funding.

Best Practice: Cost recovery policies should be developed, periodically reviewed, and adjusted as needed to meet the needs of the repository and its stakeholders.

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SECTION I: REPOSITORY INFORMATION MANAGEMENT SYSTEMS

I1. GENERAL

Effective tracking systems should be in place to ensure that *specimens* can be tracked accurately from the site at which they are collected through their entire *lifecycle* at the *repository*. Critical components of these systems include the use of unique specimen identifiers, appropriate specimen *labels*, electronic data inventory systems for specimen tracking, consent form and/or permit tracking, and other features that are described in detail below.

I2. INVENTORY SYSTEMS

A computer-based inventory system should be in place to track the location and pertinent *annotation* of every specimen in the repository. The system should also track significant events such as specimen thaws, receipt, *processing* delays, destruction, movement of the specimen within the repository, and specimen *distribution* and return (if applicable). Full query capability for all data stored should be provided.

Procedures for validation and documentation of the IT system including backup routines should be developed and included as part of a Quality Management System. *Audit* trails, software bug tracking, troubleshooting/help desk functions and resolution procedures, and IT security and access policies and procedures should be documented and maintained (see Sections D4.2. Types of Documents of the Quality Management System and D5.1. Recordkeeping).

The system should have the capacity to assign a unique ID to each specimen entered in the *database* and track its lineage (parent specimen to child to grandchild, *etc.*). If an ID exists but a new specimen ID reflective of the inventory system into which the specimen is being entered needs to be added, the inventory system should be able to track the original specimen ID as well as the newly assigned one.

Selection of an inventory system depends on a number of factors that are unique to each repository. Among these the most critical are cost of ownership, fitness for purpose, time to implementation, and ongoing support. Repositories can choose from a range of commercial off-the-shelf software programs or purchase a customized system. ISBER has developed a checklist to assist in selecting the best fit (see Appendix A: Internet Resources).

Best Practice: Specimens received in the repository should be given a printed label including both a barcode and specimen ID, if one is not already on the specimen *container*.

Best Practice: Inventory systems should allow for different reports of data elements to facilitate research questions and *collections* management. Systems should have the capability of linking specimens with associated data (*i.e.*, clinical, demographic, pre-analytical).

I2.1. Specimen Location

Each freezer, refrigerator, room temperature storage cabinet, or other unit appropriate to the collections should have a unique identifier. A convention should be established for numbering shelves, racks, boxes, as well as each location within the storage container. Certain storage systems *(e.g.,* straws) are stored in containers such as goblets and the database should be able to capture such containers that do not follow the normal box/row/column configuration.

Each location combination *(e.g.,* building, room, freezer, rack, box, row, column) should uniquely identify a location in the repository. Fixed compartments in liquid nitrogen tanks and upright freezers need to be uniquely identified as well as the boxes placed in these compartments. For example, straw sample locations in boxes are linked to racks or compartments in the freezer. The inventory system should support different storage environments for the same repository and should also record the container type (*e.g.*, vial, straw, slide). The inventory system should be able to report on available storage space and able to assign and reserve space for incoming specimens.

Changing the location of a specimen should be tracked in the Audit Trail (see Section I2.5. Audit Trail). The system should allow for mass movement of specimens with a single option to quickly and efficiently document required movement of large numbers of specimens (*e.g.,* when a freezer fails).

Best Practice: The properties of the freezer or other storage unit should be maintained in the system (*e.g.,* type, location, temperature).

Best Practice: To audit (*i.e.,* Quality Control) specimen location, a randomly generated specimen list should be checked on a subset of the stored

specimens on a regularly scheduled basis to ensure that the correct specimens are in the location specified by the inventory system.

I2.2. Specimen Descriptors

The inventory system should track specimen type; vial or container type; specimen amount; date and time of specimen collection, timestamps for receipt and/or processing; processing method; storage temperature; preservatives; and any other characteristics needed for the collection. Information should be included on the history of specimen processing and movement, including the location of shipments to and from external sites. Finally, any information about the specimen being compromised in any way should be recorded and available to the user.

The inventory system should also be able to store data that are important to the study or protocol to which the specimens belong. Having this study-specific data stored with the specimens will enable users to utilize the data for specimen selection, reporting, and other activities at the repository. Also, conditions listed in permits for the original collection of the specimens may require provision of information to the provider country.

I2.3. Information for Human Repositories

When dealing with human specimens, information relating to the following data may be maintained for a repository depending upon the nature, purpose, and type of the resource (if relevant, available, or not stored in another interoperable information management system):

- *Donor* information: age of donor at the time of collection, sex, race, ethnicity, occupation, visit number, etc.
- Diagnosis: anatomic site (*e.g.*, breast), tissue type (*e.g.*, normal), diagnosis (*e.g.*, fibrocystic disease), and modifiers to provide additional detail regarding the diagnosis. It may be important to document the gross diagnosis (what the specimen was thought to be when collected, *e.g.*, breast-normal), the pathological diagnosis (diagnoses rendered by pathology for the actual resection, *e.g.*, breast-malignant-adenocarcinoma-ductal), *quality control* diagnosis of the specific specimen obtained for research (*e.g.*, breast-normal-fibrocystic changes), and the pathologic stage at time of surgery. In some situations, it may also be appropriate to provide the diagnosis code (ICD10) and the text of clinical diagnosis.
- Diagnostic procedure: type of procedure (*e.g.*, surgery), date of procedure, procedure details (*e.g.*, mastectomy), procedure identification number (*e.g.*, surgical pathology number).
- Type of specimen collected: tissue, blood (indicate type of vacutainer tube), saliva, cerebrospinal fluid, genital fluids, etc.
- Availability of other specimens (*e.g.*, normal vs. diseased tissue, other tissues, blood, buffy coat, serum, plasma, paraffin embedded tissue, H&E slide, formalin fixed tissue, DNA, RNA, urine, feces, saliva, ascites fluid and synovial fluid) from the same donor.

An inventory system may also be designed so that digitally scanned *documents* are included such as pathology reports, H&E slides of tissues collected, clinical lab reports, donor consent forms, and *material transfer agreements* (MTAs, see Section M2.5. Material and Data Transfer Agreements).

The information stored will vary according to the purpose, nature, and intended uses for the specimen collection. Since a repository may track specimens of many different studies, consideration should be given to what the inventory system can contain and what should be stored in an external database and linked to the inventory.

I2.4. Information for Biodiversity, Environmental, and Veterinary Specimens

Many items listed in I2.3. can also be applied to the information tracked for biodiversity, environmental, and veterinary samples, specifically animal samples, as well as additional information not included above. The Global Genome Biodiversity Network (GGBN) has developed the GGBN Data Standard for standardized data exchange which lists some of the information that is important when collecting for animal/fungal/plant/microorganismal biobanks or ESBs. The VeNom (Veterinary Nomenclature) Codes developed by the VeNom Coding Group is a list of terms that are used in veterinary practice and have been standardized across institutes to

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facilitate academic discussion, research and clinical auditing. See Appendix A: Internet Resources for more information.

Natural history collections use globally unique specimen identifiers for their specimens and samples, usually accomplished through the so-called 'Darwin core triplet' (institution:collection:specimenID). The Global Registry of Biodiversity Repositories offers a curated list of such institution and collection codes (see Appendix A: Internet Resources).

I2.5. Audit Trail

The inventory system should include a full audit trail of changes made to the database. This includes recording changes to both specimen data and system metadata. The audit trail should include but not be limited to: the original data; the changed data; who made the changes; and how the change was made, date and time of change, and if possible, why the changes were made. This audit trail should be automatically recorded and available for read-only access. The audit trail data should be able to be reported electronically.

Record changes should not obscure previously recorded information in the audit trail. Such audit trail documentation should be retained for a period at least as long as that required for the electronic records and should be available for audit (see Section D7. Internal Audits).

If Personal Health Information (PHI) or PII is stored in the system, an additional audit trail may be required by the relevant legislative authority. In these cases, every instance of viewing or reporting the data should be documented in the audit trail with the date, time, and name of the person viewing or reporting the data. If an individual requests a list of all persons viewing their PHI or PII, the system should be able to provide that data.

I2.6. Risk Assessment and Security

Access to the computerized inventory system should be tightly controlled. Security roles with defined privilege levels should be assigned to individual users of the system. Some individuals may be able to view specimen availability whereas others can enter or modify specimen descriptions and make requests to have specimens shipped from the repository. All PHI or IACUC should be secured within the inventory system through access controls and/or encryption. All remote communication should be able to be conducted on an encrypted socket.

Best Practice: The system should provide a mechanism to log off users after a specified period of time of inactivity.

Best Practice: The inventory system should provide for single sign-on utilizing the operating system's user name and password if possible.

Best Practice: Repositories should use a computerized inventory system that includes a layered approach to security in which the system, application, transmission, and network are secured. The repository system should be isolated from other systems that might be compromised.

Best Practice: Passwords should conform to the minimum institutional standards.

I2.7. Interoperability

Within modern repository informatics systems, integration and interoperability are highly desirable. Systems should be able to integrate with other local applications such as electronic medical records, cancer registries, pathology systems, and freezer temperature monitors. This allows other systems to be the Single Source of Truth (SSoT) for appropriate data.

Integration and interoperability have many benefits including, but are not limited to the following:

- Reduced re-entry of data. Every time data are manually reentered from one system to another there is a risk of error. Re-entering of data can be costly.
- Data errors found and corrected in the SSoT system need not be replicated to other systems.

Data should be electronically convertible into formats that can easily be shared among collaborating institutions, where possible and appropriate. The inventory management system should enforce all data integrity, security, and audit trail requirements for external access. To achieve interoperability, inventory management systems should include the following:

- Public documented Application Programming Interface (API) to enable other systems to integrate with it.
- Common public vocabularies for relevant data points (*e.g.*, SNOMED, ICD9-CM, ICD10, ICDO).
- A framework that allows it to connect to other systems and to communicate with external APIs on an event driven or periodic basis.
- A security policy to ensure proper sharing of data.

I2.7.1. Data Exchange Standards

In recent years, a sector of human biobanks related to the medical/clinical community has developed two main data standards. The first standard is BRISQ (Specimen Reporting for Improved Study Quality[1], a 3-tier standard to better understand, interpret, compare, and reproduce experimental results, which involve human specimens. The second standard is SPREC[2,3], a standard to share pre-analytical data related to collection, processing, and storage through assigned codes.

Other data exchange standards that have been developed are:

- Minimum Information About Biobank data Sharing[4] provides information about the sample collection and study of human specimens.
- GGBN Data Standard[5] enables standardized exchange of DNA and tissue sample data and fulfills the requirements of the Nagoya Protocol.

Natural History Data Standards:

- Darwin Core (DwC)[6]
- Access to Biological Collection Data[7]

I2.8. Cloud Computing

Cloud computing and storage solutions are Internet-based services that offer on-demand, online access to shared computing resources with varying levels of functionality depending on the users' requirements, ranging from mere data storage to complete software solutions (*e.g.*, a Repository Inventory Management system), platforms to simplify the ability of application developers to create new products, and entire computing infrastructure for software programmers to deploy and test programs. Cloud services providers (CSPs) are generally an entity separate from the repositories and provide various capabilities to store and process data in either privately owned or third-party data centers that may be located far from the user. A repository that engages a CSP should understand the cloud computing environment and conduct risk analysis and establish risk management policies as well as enter into an appropriate business associate contract or agreement and a service level agreement.

Repositories seeking information about types of cloud computing services, cloud data management data interface, and technical arrangement options may consult a resource offered by the National Institute of Standards and Technology (NIST, 2014) or the International Organization for Standardization (ISO/IEC 17826-2016) (see Appendix A: Internet Resources).

Best Practice: Repositories should ensure that any cloud service providers utilized are compliant with regulations that maintain the privacy and security of ePHI and PII.

I2.9. Reporting

The information management system should have the ability to produce reports to support the repository workflow, document adherence to standards and practices, and provide any business metrics required by the repository.

The system should provide the user with an interface for specifying display content and search criteria for the report. The exact nature of this interface can vary from full "what you see is what you get" (WYSIWYG) report designers to simple field selection for tabular reports. The query editor can also be presented utilizing several approaches, including simple data query forms, Query By Example screens, customized query builders, and text areas for native query specification.

The information management system should have the ability to save report specifications for future execution. The system should also have the ability to edit these saved specifications as well as share the specifications with other users.

The inventory system should have the ability to

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generate report output and electronic data files (*e.g.*, in ASCII, XML, CSV, or XLS). The system should provide full access to the database for reporting, provided that the system's security rules are enforced. This access will allow users to generate reports on inventory status, freezer status, user access, audit trail entries, and other data tracked by the database to meet their needs.

If the database contains PHI records, the security model should restrict reporting on confidential data to only authorized users. Additionally, the repository should maintain SOPs about the generation, use, and destruction of reports that contain PHI and PII to ensure that donor confidentiality is maintained.

I2.10. Validation

Whether the inventory system is a commercial off-the-shelf software or a customized bespoke system, the repository should employ procedures and controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records. Such procedures and controls should include the following:

- Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.
- Protection of records to enable their accurate and ready *retrieval* throughout the records retention period.
- Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.
- Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access an operation or computer system input or output device, alter a record, or perform a specific operation.
- Use of checks to determine, as appropriate, the validity of the source of data input or operational instruction.
- Determination that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform the assigned tasks.
- The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures to deter record and signature falsification.
- Use of appropriate controls over systems documentation including:
    - Adequate controls over the distribution of, access to, and use of documentation for system operation and maintenance.
    - Revision and change control procedures to maintain an audit trail that documents time-sequenced development and modification of systems documentation.

In addition to validation at the initiation of the system, ongoing validation should be performed when the system is updated in a maintenance release or new features are added. The amount and depth of validation necessary is dependent on the scope of the update. Modified portions of the system should be re-tested in order to ensure that no regression errors have been introduced. New features should be validated if they are going to be utilized.

Best Practice: All validation performed should be documented to ensure traceability and ongoing accuracy of the system.

I2.11. Quality Assurance

In order to provide high-quality information to serve the tracking system, standards, policies, and procedures should be used to ensure and maximize the accuracy and completeness of the data. Periodic reviews of data quality issues and adjustments to programs and processes will ensure continuous quality improvement. The electronic inventory system should comply with industry-applicable GP guidelines (see Section D6.1. Good Practices). An established *Quality Assurance* program for the inventory system should be primarily directed at prevention of non-conformances as well as detection, corrective action, and process improvement implementation.

Regular Quality Assurance audits and reviews should completely assess:

- User requirements, as well as industry-specific certification requirements.
- Details of the review and approval process for

software developed in-house or obtained from a third party.

- Procedures followed to test the software functionality compared with user requirements.
- Corrective actions or processes used to handle program errors and modifications.
- Training provided to personnel associated with the use (and development, if applicable) of the inventory system.
- A quality manual on the quality assurance of a repository's database.

Best Practice: A periodic audit of the database should be performed to ensure accuracy of data.

I2.12. Backup

The database should be backed up on a regular basis, depending on the institutional policies and frequency of data modification. The more frequent the data is changed, the more frequently the backups should be made.

The procedures to preserve the integrity of repository data should include (but are not limited to) steps to limit the extent of the destructive event, protocols for periodic backing up and storing of information, procedures for off-site storage of backup data, and protocols/procedures for restoring information from backed up media.

The backup procedures should specifically address the recoverability of information. Backups should be tested on a regular basis to ensure the data can be accurately recovered.

Best Practice: Repository databases should be backed up frequently (*i.e.*: daily, weekly) based on institutional protocols or frequency of database modifications.

I2.13. Labels

Each specimen should receive a label that tightly adheres under all planned storage and processing conditions. Information printed on labels should be resistant to all common laboratory solvents. Labels should contain an ID linking to a database containing details about the specimen collection and processing information (see Section I2.2. Specimen Descriptors). Flexibility should be allowed in the location and size of the label to allow for label legibility on a wide variety of containers.

Material used in composition of containers for some specimens may pose special problems for label adherence and therefore, in some cases, the label should be able to adhere to itself.

The adherence of labels to containers as well as the use of particular types of ink should be tested under conditions more extreme than the anticipated storage and processing conditions before they are put into regular use.

I2.13.1. Labels for Specimens

Specimens should be labeled in such a way that protects privacy and confidentiality and is in compliance with applicable laws and institutional policies. Specimens should be labeled with a unique code or ID not derived from personal information of the donor. No other study or personal health information should be encoded in the specimen ID. Depending on the type of repository, essential information such as genus and species or other details may be part of the label.

Best Practice: For all specimens, the repository's unique identifier for each specimen should be printed on the label in both barcode format and/or human readable form. The ID should not be reflective of its storage location in the repository, as locations may change over time.

I2.13.2. Barcoding

Whenever possible, labels should be printed with a barcode that uniquely identifies the specimen and links to the database with the relevant metadata about the specimen.

I2.13.3. RFID

Radio-Frequency Identification (RFID) tags may be used instead of barcoded labels. The identifier stored in the RFID tag must be linked in the database with the relevant metadata about the specimen, in the same way a barcode is.

I2.14. Shipping Log

For more details on shipping, consult Section J: Packaging and Shipping. Each repository should maintain a shipment log to record the receipt and

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dissemination of shipments sent from the repository. This log should be integrated into the functionality of the inventory management system described above. Each shipment entry should be given a unique shipment ID. The electronic log should be able to track the following elements:

- Shipment/Invoice ID
- Source
- Destination
- Date shipped and date received
- Courier name
- Package Tracking ID, if applicable
- Unique specimen identifier
- Specimen type(s)
- Genus and species or family (if required)
- Material Transfer Agreement
- Quantity sent and received
- Study name and/or number if available
- Shipping conditions (*e.g.*, dry ice, room temperature)
- Name/Signature of individual receiving the shipment
- Any discrepancies between the *shipping manifest* and the actual shipment
- Any indication that a specimen has been compromised (*e.g.*, record *deviations* in specimen quality upon receipt)

CITATIONS

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SECTION J: PACKAGING AND SHIPPING

J1. GENERAL

Packaging and shipping should conform to applicable regulations. For example, air shipments should conform to International Air Transport Association (IATA) standards and ground shipments should conform to applicable national/federal standards. All personnel involved in shipping biological materials should be appropriately trained (IATA/Department of Transportation, Alternative Dispute Resolution, and other standards relevant to shipping and transport).

J2. TRANSPORT SPECIFICATIONS

The first step in the preparation of a shipment for transport is the determination of the specifications for the *specimens* to be shipped.

J2.1. Regulatory Requirements

The shipper should first determine how to classify the specimens that are to be transported. Specimens such as infectious substances, diagnostic specimens, biological products, genetically modified organisms and microorganisms, or toxic substances may be considered dangerous goods. Also, the preservatives and excipients that have been applied to the specimens may be considered as toxic, flammable liquid, non-flammable gas, or corrosive, all of which are dangerous goods. National or federal transport regulations as well as those from their International Civil Aviation Organization (ICAO) and IATA should be consulted in order to properly classify the specimens to be included in a shipment.

Non-human specimens must be checked for CITES (Convention on International Trade in Endangered Species of Wild Fauna and Flora) regulations. Depending on shipping origin and shipping destination, CITES documentation must accompany the specimens and be clearly marked with CITES labels. Only registered organizations are allowed to send out or retrieve CITES material with a notable exception of when shipping CITES material within the European Union.

Many countries require that personnel involved in the transport of dangerous goods receive training in this area before they begin their shipping responsibilities. As regulations change, training may need to be updated.

J2.2. Temperature Requirements

To preserve specimen quality, shipment temperature should be tracked (when possible) and *documented* and any fluctuations in temperature should be minimized. The staff preparing shipments should be trained and understand the conditions required for shipping different types of specimens.

The following are typical temperature conditions required for transport of specimens and the insulation/refrigerant helpful to maintain that temperature:

- Ambient (20 to 30°C) - insulated packaging to protect from extreme heat or cold ambient conditions.
- Refrigerated (2 to 8°C) - wet ice or gel packs (conditioned at –15°C, designed for refrigerated temperatures, or phase change material rated for refrigerated transport).
- Frozen (-20°C) - gel packs designed for frozen temperatures; conditioned at or below -20°C.
- Frozen (-70°C) - dry ice pellets, blocks, or sheets. Note that dry ice (solid CO_2) employed for frozen shipments is considered a hazardous material and appropriate labeling should be included.
- Frozen (at or below –150°C) - *liquid nitrogen dry shipper,* also referred to as a vapor shipper. Dry nitrogen shippers are insulated *containers* that contain refrigerated *liquid nitrogen* that is fully absorbed in a porous material, and is therefore considered a non-dangerous product and is not subject to IATA regulations as a dangerous good (special provisions A-800) if properly filled (*i.e.*, no free residual liquid nitrogen remains).

Best Practice: Shipments of cold or frozen material should be shipped with sufficient and appropriate refrigerant to maintain temperature throughout the shipping cycle with allowance for at least a 24-hour delay in arrival time.

Best Practice: Shipments of specimens with high value or those with critical temperature requirements should include a temperature-recording

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device (*e.g.*, datalogger, temp card) that can verify the temperature of the material being shipped throughout the transport cycle.

J2.3. Humidity Requirements

Specimens sensitive to humid conditions may need to be shipped in sealed bags with desiccant to prevent exposure to moisture during transit.

J2.4. Arrival Time Requirements

Time sensitive specimens such as fresh whole blood should be consigned to couriers with a proven reputation of successful on-time delivery (see also Section J5. Cold Chain). Time required for shipment *processing* should be considered as well. Shipments should be initiated when there are at least two working days left in the week after the estimated delivery date, in case they do not arrive on the day scheduled for delivery. Shipments should also be scheduled so that they do not arrive at the recipient location on a holiday or weekend. Attention should be paid to weather forecast when planning a shipment to ensure the shipment is not delayed due to bad weather conditions.

J2.5. Packaging Shipments

The quantity of specimens to be transported will affect the type of packaging and amount of refrigerant required to maintain appropriate temperatures for all specimens in the shipment. The container should be appropriate (*i.e.*, validated) and of the right size for the number of specimens and amount of refrigerant that will be included in the container. Shipments involving a large number of specimens may be divided into multiple, smaller shipments to minimize risk or accommodate available containers.

J2.6. Other Packaging Considerations

- Specimens should be positioned between the refrigerants used rather than being placed on top of or underneath the refrigerant.
- After the specimens and the refrigerant have been placed into the container, empty space should be filled with Styrofoam or wadded paper to prevent movement of the specimens during shipment.
- Any *labels* remaining on the exterior of the shipping container from a previous shipment should be removed or marked through.
- Air-bills should not be reused.

J3. VERIFICATION OF SHIPPING CONDITIONS

J3.1. Review of Packaging Test Report

The shipper is responsible for choosing appropriate packaging for the shipped material. The shipper should review all test reports for the packaging to ensure that the packaging regulations are met.

Packaging that has undergone stringency (*i.e.*, validation) testing should be used in the same configuration under which it was tested. Tests may include measuring all parameters that could influence specimen integrity (*i.e.*, temperature, humidity, light sensitivity, structural quality, spill containment).

J3.2. Test Shipments

In some situations, especially relating to extremely valuable *samples*, repositories may choose to first send a test shipment that approximates the characteristics of the actual shipment. This may inform the shipper as to the adequacy of packing coolants and also serve to identify any potential obstacles for the successful shipment.

Best Practice: A temperature-recording device or an irreversible temperature indicator should be used during shipping tests to ensure that temperature requirements have not been exceeded.

J3.3. International Shipments

Special permits or other requirements may be unique to certain nations and regions, including regulations related to ethical issues that prohibit the import/export of certain types of human specimens or have specific requirements concerning the import/export of such specimens. Special permits such as the CITES permit and additional paperwork may be required for field *collection* of organisms that are endangered or protected.

Most international shipments also require a customs clearance note to be clearly displayed on the outside of the package. Identification of all national/

federal requirements for shipping should be performed prior to the initiation of the shipment. Use of a customs broker can be helpful or even critical. Certain couriers can provide this service, which can be essential for transport to/from a foreign country.

Best Practice: Due to possible delays in completing customs requirements, temperature-sensitive material should be consigned with a courier capable of replenishing refrigerant in the event of a delay. As a precaution, three additional days' worth of refrigerant is recommended for shipments in cases where customs clearance may be difficult.

Best Practice: International shipments should include a letter on institutional letterhead (as appropriate) documenting the contents and handling requirements. Copies of all import permits and sanitary certificates should be included, as needed.

J4. TRACKING SHIPMENTS DURING TRANSPORT

Both the shipper and recipient should track all packages while in transit.

J4.1. Notification of Shipment

The shipper should notify the recipient that a shipment is scheduled to arrive on a specific date. The recipient should confirm that they are able to receive the package and that they have the proper facilities for storage before the shipper releases the shipment. The shipper should provide a 24-hour emergency contact for all packages transporting dangerous goods.

J4.2. Shipping Manifest and Tracking Number

The shipper should send a *shipping manifest* (preferably electronic) to the recipient prior to the release of the shipment. A paper copy should also be included with the shipment itself. The tracking number should be provided to the recipient as soon as this is available.

J4.3. Sample Receiving and Verification

Confirmation of receipt and the condition upon arrival should be documented using a Verification Report Form for every delivery or shipment of specimens. This form could originate from the shipper or recipient. If originating from the shipper, it should be sent with the shipment/delivery. The Verification Report should be sent to the shipper and any discrepancy between specimens sent and received should be immediately resolved.

J5. COLD CHAIN

J5.1. General

The cold chain is the temperature-controlled supply chain (below ambient), which must remain unbroken over a series of collection, storage, and *distribution* events (from field, to *repository*, to other research institutions). The purpose of the cold chain is to safeguard perishable specimens and preserve specimen quality and integrity. Cold chain temperatures range from +4°C to -196°C, depending on the specimen type shipped and the intended use.

The cold chain distribution process is an extension of the Good Manufacturing Practice (GMP) which all drugs and biological products are required to adhere to by various health regulatory bodies. The same principles apply for animal and plant specimens. As a result, all distribution and storage processes should be validated to ensure that there is no negative impact on the quality of the specimens.

Best Practice: The management of cold chain should include all measurements, qualifications, validation, and corresponding documentation. All components and operations should be demonstrated to perform reliably.

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J5.2. Cold Chain Validation

Cold chains need to be validated in advance and controlled. Test runs are recommended, when feasible:

- Logistics Providers: specialist couriers, carriers, and logistics providers should have the technical ability to link with airlines for real time status, generate web-based export documentation, and provide electronic tracking. Providers should also offer on-the-ground troubleshooting, where possible.
- Transport and Shipping *Containers*: a wide variety of refrigerated vehicles, warehouses, insulated shipping containers, and other specialized packaging are available. These containers/packages should be tested and evaluated to be fit-for-purpose and/or compliant with appropriate shipping regulations for packaging class and dangerous goods transportation (*e.g.*, flammable preservatives, dry ice, ICAO, IATA, road [ADR], rail [RID], maritime regulations) (see Appendix A: Internet Resources).
- Tracking: temperature data loggers, and/or other devices (*e.g.*, thermocouple probes, RFID tags, color-coded vaccine labels) should be used when collecting samples and specimens in the field destined for shipment. The purpose is to monitor and record temperature and handling history from field to repository.
- Documentation: each step of the custody chain should follow established protocols and maintain proper records. To avoid customs delays due to inaccurate or incomplete customs paperwork, guidelines for creating all necessary commercial invoices, etc., should be strictly followed.

SECTION K: SPECIMEN COLLECTION, PROCESSING, RECEIVING, AND RETRIEVAL

K1. GENERAL

Specimen collection and *retrieval* practices have many elements in common, while specimen *processing* will vary according to the specific research or clinical activities associated with the *repository*. Specimen availability and potential analytical objectives for their utility should be considered prior to initiating specimen collection and methods should be used to ensure that all specimens collected are *fit for purpose* (see also Section E1. Validation of Sample Processing Methods).

It is important to ascertain the sensitivities of different types of specimens and associated *analytes* to collection, processing, storage, and retrieval *procedures*. These may vary, particularly between viable and non-viable specimens; therefore, when appropriate, collection protocols should be consistent and incorporate any special requirements necessary for the *preservation* of viability, functionality, structural integrity and stability of cells, tissues, organs, cell-free fractions, macromolecules, and/or analytes. In addition to specimen type, other considerations prior to initiating a collection include: regulatory, *safety*, and legal/ethical issues.

Specific personnel responsibilities, training, risk management, and skills may be required for specimen collection. Planning of collection logistics should take into account distance from the collection point to the processing lab, interim transport containment, and security of the storage facility (if this is a different location). Standard protocols for specimen collection and *sample* handling should be established and followed. Protocols for stabilization and/or preservation of samples during transit may be necessary.

Due to the potential impact of pre-analytic processes on specimen quality, it is important to apply strategies that maintain the stability and functionality of biospecimens and macromolecules of interest (see Section E1. Validation of Sample Processing Methods). Stringent procedures are similarly required for specimen labeling and tracking from the point of collection to processing and storage in the repository, shipment to and *receipt* at the site of analysis, and final specimen *disposition*.

Based on availability, many different specimens may be collected, processed, and/or stored from the same source (*e.g.*, solid tissue, blood, saliva, urine) even longitudinally over time. Furthermore, specimens may be processed into a variety of formats (*e.g.*, formalin-fixed paraffin embedded [FFPE], optimal cutting temperature [OCT] blocks, snap-frozen, viable cell fractions, *lyophilized* fractions). Redundancy of specimen types can maximize the opportunity for future usage; however, limitations imposed by processing time requirements and the repository's storage capacity must be considered when collecting multiple specimen types and processing them in a variety of formats.

Best Practice: Multiple fit for purpose specimens should be collected. When possible, multiple aliquots should be made and stored separately to minimize the risk of compromised sample integrity or freeze/thaw events.

Best Practice: The time, temperature, and the person handling the sample should be documented every time the specimen is manipulated.

K2. PILOT STUDIES AND PROOF OF PERFORMANCE STUDIES

When possible, small-scale pilot studies should be employed to assess feasibility and to optimize and validate new protocols, equipment, and laboratory processing methods. Pilot or feasibility studies can identify problems or critical points and instigate preventative actions at an early stage of collection, handling, and processing before a larger study is undertaken. Pilot studies can also help optimize new processes and identify training required before implementing a new protocol. These studies are a requirement in some countries.

Best Practice: Repositories should formalize and document test plans used for evaluating the performance of equipment or validating a processing method.

K3. SPECIMEN INTEGRITY

The relative importance of the period of time between receipt, processing, and storage of a specimen depends on its intended use and application. Biological specimens can lose functionality and molecules can degrade at different rates dependent upon type and status of *donor* and collection circumstances[1,2]. It is important to identify critical factors which predispose different specimens to deterioration and contamination. For example, for specimens from vertebrate animals, cellular integrity and molecular degradation may begin when the vascular supply to an organ is interrupted during surgery (*warm ischemia*)

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or when tissue is removed and placed in a cold *container* (*cold ischemia*). The speed at which the degradation occurs will depend upon many complex factors including, but not limited to: donor, organism, and/or organ health status, type of organ and tissue, collection procedures, the temperature and hydration at which the specimen is maintained, as well as the stability of the molecules of interest[3]. Tissue specimens should be maintained at optimal temperatures, as specified by the collection protocol. In general, specimens should be processed as rapidly as possible with minimal manipulation.

Best Practice: All pre-analytical procedures including collection, processing, storage, and shipping should be documented since pre-analytical variables may affect analytical results.

Best Practice: End-users should be provided with the recorded pre-analytical variables so that informed, evidence-based assumptions and conclusions about the experimental data can be made.

K3.1. SPECIMEN STABILITY

Specimen stability may be affected by parameters such as the use of anticoagulants and stabilizing agents like ethylene diamine tetraacetic acid (EDTA) in blood and ascorbate in urine[4,5]. It is important to know in advance the specimen collection requirements by manufacturers of specific assay kits. For some applications, rapid *dehydration* is an effective method to stabilize molecules. Dehydration methods may be more practical in field settings where access to refrigerants or chemical fixatives is dangerous, cumbersome, or unavailable.

Specimen stability is also detrimentally affected by exposure to the environment. Excessive ultraviolet rays can alter DNA or RNA structure; excess humidity can lead to mold; untreated atmospheric air may oxidize protein and other metabolites; and a large sample volume to container dead-air volume may alter pH, as well as create an inefficient storage solution. An important variability factor in pre-analytical procedures is time: collection time, processing time, or long-term storage time. The impact of this time can be assessed by short- or long-term stability studies. A standardized tool has been developed to facilitate these studies (*e.g.*, body fluids) (see Appendix A: Internet Resources).

Best Practice: Selected methods for collecting and preserving specimens should be followed to ensure that any preservatives, dehydration, or other protective treatments used do not have a deleterious effect on future analyses.

K3.2. TEMPERATURE

Because cold preservation is a critical stabilizing factor for many specimen types, the temperatures at which specimens are collected, processed, and stored should be carefully considered and documented[6,7]. These range from chilling/hypothermic (2 – 8°C) to low subzero (-4°C to 0°C), freezing (-20°C to -150°C) in mechanical/electrical freezers and storage at the ultra-low temperatures of liquid and vapor-phase *liquid nitrogen* (to a minimum of -196°C). Choice of collection and storage temperature depends upon impact to specimens from chilling, freezing, and cold-induced dehydration; duration of exposure and tolerance to cryoprotective treatments; and intended analyses. The general rule is that a warm storage environment, even for a short period of time, can lead to physiological stress and macromolecular degradation. For this reason, it is necessary to maintain appropriate temperature(s) from the point of collection through processing and storage. Hypothermic temperatures (2 – 8°C) have generally been considered as the default condition for specimen transport/storage when not frozen; however, for some processing/applications the ambient temperature is recommended. Consideration of downstream assays is critical, as biological specimens may react to hypothermic conditions by changing their metabolic and molecular profiles.

The type and duration of low-temperature exposures are also dictated by the intended use of the specimen. For example, blood samples collected to yield serum will need to be maintained at room temperature to allow clotting. The collection and processing time should be documented and reported to the end-user. This information is critical for *quality control* measures (*e.g.*, will help explain the presence of fibrin, a common occurrence when insufficient time is allowed for clotting to occur).

Specimens can also be collected, shipped, and stored at ambient temperatures using new technologies that have been developed specifically for such purposes (see Section C7. Ambient Temperature Storage). Ambient preservation is available for purified analytes (RNA and DNA)[8] as

well as for more complex specimen types (*e.g.*, saliva, feces, blood, cells, tissue). Preservation duration can range from a few days to, in some cases, greater than 25 years[9]. Technology for preserving dried blood spots on cellulose-based cards/filter papers at ambient temperature for longer than 15 years has been well described in literature[10].

Best Practice: Continuity of the *cold chain* should be maintained and documented from the point of collection to deposition in the repository and to eventual use.

K3.3. Biopreservation/Cryopreservation

Biopreservation is a general term used to describe the preservation of biological materials of all types (*e.g.*, living cells, tissues, fluids, organs, organisms) using a variety of fixation/preparation techniques and a range of low temperatures or ambient storage methods. *Cryopreservation* is a more specific form of preservation that involves the storage of specimens (*e.g.*, living cells, tissues, fluids, organs, organisms) at their optimum ultra-low temperatures. Cryopreservation of tissues and fluids involves storage at temperatures low enough to stop most enzymatic or chemical activity (*e.g.*, storage below -136°C, the *glass transition* point of polyol's water solution).

K3.3.1. Biopreservation

Common methods of biopreservation (excluding cryopreservation and storage at ultra-low temperatures, discussed in more detail below) include chemical fixation (*e.g.*, in 10% formalin, in alcohol) or *desiccation* within a preservation matrix at ambient temperatures. From mummification to modern techniques, tissue fixation is the oldest way to preserve tissues and organs. A common tissue specimen preservation technique involves fixation in a formalin solution with subsequent embedding of the fixed tissues into paraffin, creating an FFPE tissue block. This technique has been used for the past 100+ years for morphological assessment of tissue structure and, more recently, for the preservation of molecular analytes (*e.g.*, proteins, DNA, RNA). Frozen samples may be processed to FFPE blocks. This conversion should always be documented, as it may affect its fitness-for-purpose. Another common clinical technique is preservation of dry blood spots on paper or other matrix. Once dried, the sample's nucleic acids, metabolites, and proteins could be stable for months to years at ambient temperature or under refrigeration. Other methods include biofluids concentration and preservation on a dry matrix (*e.g.*, dry concentrate of urine or its components on a membrane), vacuum drying, and freeze drying.

K3.3.2. Cryopreservation

Cryopreservation of viable cells and tissues involves the process of cooling cells or whole tissues to ultralow temperatures at which any biological activity, including the biochemical reactions that would lead to cell death, is effectively stopped (*e.g.*, storage below -136°C, the glass transition point of polyol's water solution). There are two distinct methods of cryopreservation: (1) preservation in the frozen state which can involve either immediate freezing (also known as snap-freezing or ultra-rapid freezing) or controlled-rate (slow programmable) cooling and (2) *vitrification*, which is preservation in the glassy, non-crystalline state. Both methods may require the addition of *cryoprotectants* which have different protective properties (colligative or osmotic), although generally they will lower the freezing temperature. Cryoprotectants are applied in different regimens, combinations, and concentrations dependent upon the mode of cryopreservation (frozen or vitrified).

In contrast to snap-freezing, controlled-rate cooling of cells/tissues/organs minimizes the potential for lethal, intracellular ice to form during the freezing process controlling extracellular *ice nucleation* (also termed 'seeding') and applying optimally slow cooling rates that allow sufficient water to leave the cell during the progressive freezing of the extracellular fluid. Controlled-rate cooling requires the careful control of cooling rate (*e.g.*, around 1°C/minute is appropriate for many mammalian cells), ice nucleation temperature and terminal freezing temperature and hold time (*i.e.*, before specimens are transferred to LN_2), the optimization of which will vary between cells of differing size and water permeability. To circumvent cryoinjury caused by toxic cell volume changes and the excessive concentration of solutes,

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the application of colligative cryoprotectants, such as dimethyl sulfoxide (DMSO), is required during controlled-rate cooling.

A 1°C/minute cooling rate may be achieved for some cells using devices such as a rate-controlled freezer or a bench-top portable freezing container. For other cells, a device in addition to a cryoprotectant is preferable. Alcohol-based or alcohol-free portable devices are commercially available and may also be customized as a 'do-it-yourself' device[11,12].

Vitrification is a process that avoids the potential damage to cells caused by intracellular and extracellular ice formation by the addition of cryoprotectants at higher concentrations which increases the viscosity of the sample and prevents ice crystals from forming.

Common cryoprotectants, such as DMSO, ethylene glycol, or propanediol[13] are often toxic in high concentrations and care must be taken to limit the damage produced by the cryoprotectant itself. When possible, researchers should test available preservation solutions to determine which is optimal for their specific research activities and, as required, pilot test the cryoprotectant strategy for their preserved samples. Using an appropriate cryopreservation medium and cryoprotectant(s) will reduce the rate of degradation at hypothermic temperatures and offset the risks of inadvertent devitrification at ultra-low temperatures.

The temperature at which frozen and vitrified preparations are stored can affect the length of time cells can be stored before they lose viability (generally, the lower the storage temperature, the longer the viable storage period). As temperature is reduced, metabolic and degradation processes in cells are slowed; however, they are not effectively slowed to allow for long-term storage (years to decades) until the temperature falls below the glass transition (*Tg*) temperature of pure water (effectively < -132°C for most mixtures of cells and aqueous cryopreservation media). The *Tg* of some vitrification solutions can be higher and it may be prudent to determine the actual critical *Tg* using thermal analyses.

K3.4. Freeze/Thaw and Cooling/Re-warming Cycles

Freeze/thaw cycles for specimens cryopreserved in the frozen state and cooling/re-warming cycles for specimens in the vitrified state can be damaging to the macromolecules and cells intended for analysis. Damage can also occur via osmotic and dehydration injury during exposure and removal of cryoprotective additives and vitrification treatments. Therefore, it is important to select *aliquot* sizes that are appropriate for the intended uses for the specimens in order to minimize the number of times a sample is thawed and frozen or vitrified before it is used. Number of freeze/thaw cycles before processing should be minimized. Cell and tissue specimens are generally maintained at liquid/vapor nitrogen temperatures in order to achieve biopreservation of the sample below the *Tg* (below which the cell biochemical activity is virtually stopped). Thermal cycling intervals of freezers resulting in sample temperature increases above the *Tg* may lead to repeated freeze/thaw cycles even within the sub-zero frozen state.

In addition to storage temperature, handling during removal from storage will affect the viability of cells and may result in degradation of cellular components. Every time a specimen is warmed above the *Tg,* it experiences a micro-thaw event. Repeated thermal cycling episodes lead to increased cell death via apoptosis and necrosis. The temporal nature of delayed onset cell death resulting from preservation stress may affect the quality of data obtained from these specimens depending on the timing of experiments post-preservation and the ability of the cells to recover from cryoinjury in the long-term.

Moving specimens from a lower frozen state to a higher temperature during retrieval of other specimens will change the composition of the specimens in the storage container that are not retrieved but just kept at warmer temperatures for a short while. For these reasons it is essential to limit the potential of cooling/re-warming, freeze/thaw, and vitrification/devitrification cycles occurring when these or other specimens are introduced or removed from storage and during transport or shipping[6].

Best Practice: The number of freeze/thaw cycles of a sample before and after processing should be minimized and documented.

K4. COLLECTION AND STORAGE CONTAINERS

Collection and storage containers vary according to specimen types being collected, the temperature of the intended storage, and the analytical goals of the study. During selection of container type, consideration should be given to the long-term use, standardization and applicability to new platforms, and automation. Also, the same containers used for specimen collection may not be suitable for specimen storage. In some cases, contaminants associated with the container (*e.g.,* persistent organic pollutants, heavy and trace metals) may interfere with subsequent analysis. This issue is especially true for specimens stored for environmental analysis. Container *labels* or other identifying elements such as embedded barcodes should be permanent and able to endure excursions in and out of cold conditions and exposure to high humidity and ambient temperatures, especially when samples are taken from extreme environments (*e.g.*, cryogenic temperatures, heat shock) (see Section I2.13. Labels). Light-sensitive material should be stored in containers that do not allow penetration of light such as amber vials or amber-coated bags.

K4.1. Sterility and Cleanliness

Risk assessments and mitigation exercises should be undertaken in the context of a specimen's requirements for asepsis. While complete sterile conditions may not be required for many specimen collections and processing, adequate consideration should be given to the cleanliness of instruments, surfaces, and equipment used in specimen processing and handling. RNA is particularly sensitive to RNAses which may be present on tools and surfaces that have not been properly cleaned/sterilized. Contamination of microbial DNA may interfere with downstream applications and, similarly, endotoxin contamination may affect downstream functional immunological assays. Where disposable instruments are used, every specimen should be handled with fresh instruments and when non-disposable instruments are used, they should be appropriately cleaned after each specimen processing. *Sterility* of preservatives, cryoprotectants, and liquid nitrogen supplies should also be considered.

K5. COLLECTION PROCEDURES

A variety of protocols exist for the collection of different specimen types. The protocol chosen should be suited to the particular needs of the study, specimen types collected, collection locations (*e.g.*, geographic and clinical setting), and intended downstream assays. Sources of specimens may be determined by study goals, cost to implement the collection, and ease of collection. For example, tissues may be collected post-surgery or post mortem; bodily fluids may be collected from study participants; and environmental samples may be site specific. Special considerations for clinical specimen collection procedures are presented below. Protocols for the field collection of non-human specimens are often highly *taxon*-specific and recent guidelines for major eukaryotic taxonomic groups may be found in Gemeinholzer et al[14].

Best Practice: Institutional collection of human and animal specimens for research should under no circumstance interfere with appropriate patient diagnosis or care.

Best Practice: Institutional specimen collection should be reviewed by a Human Subjects Review Board/Ethics Review Committee or other appropriate ethics board (see Section L2.1. Human Subjects Review Board/Ethics Review Committee).

Best Practice: Staff should wear personal protective clothing/equipment, as appropriate, when working with specimens (see Section F5. Personal Protective Equipment).

Best Practice: Field collecting (biodiversity) should not threaten a species' or population's existence.

K5.1. Solid Tissues

The appropriate handling of tissues procured for research purposes can be facilitated by having a practicing pathologist supervise the actual procurement of the tissue; this is especially important to prevent the compromise of diagnostic specimens. Information from the pathologist on the characteristics of the biopsy or surgical material (*e.g.*, percentage normal, percentage tumor, percentage necrosis, and/or percentage fibrosis) as determined by microscopic evaluation should be obtained on a per-specimen basis and recorded. It is well known that tissue specimens are heterogeneous with respect to the percent tumor, normal, necrosis, and fibrosis. Where possible, multiple sections or samples (aliquots) should be created

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to allow for greater use of the specimens. A procedure should be in place to evaluate the characteristics of each aliquot by reviewing a representative cryostat section. Alternatively, one representative section from a determined number of sections may be reviewed.

The use of standard FFPE protocols (including properly validated fixative and timing of fixation) is important for producing optimal quality specimens. Multiple pre-analytical factors may affect FFPE specimen quality and suitability for further analyses[15].

K5.1.1. Surgical Samples

Remnant clinical specimens may be collected from diagnostic surgical procedures. With proper ethics committee approval and appropriate *informed consent*, specimens may be resected specifically for research. Policies documenting the subset of surgical specimens exempt from pathologic review are in place at most hospitals[16,17]. If the specimen in question is not exempt, it must arrive at the pathology lab intact for examination before research samples can be procured. Any exceptions should be approved by the pathologist in advance of tissue collection.

If not processed immediately, specimens should be placed in a clean or sterile container on wet ice (2 – 8°C) for transport from surgery to pathology or to the repository. It is also important to prevent cross-contamination, dehydration, and desiccation of tissues during transportation. Vacuum sealing, cooling of fresh tissues, or covering with sterile gauze moistened in biopreservation media is recommended if immediate fixation/stabilization cannot occur. The optimal procedure would be to handle all specimens in a sterile manner; however, that is not always practical, as few surgical pathology gross rooms have a biosafety hood or similar designated area. Many research protocols do not require that tissue specimens be procured or processed following sterile procedures. A "clean" area should be set up for aseptic specimen procurement/processing.

During specimen procurement, contact between different specimens should be avoided (specimen contamination) and equipment used for procurement should be replaced between different specimens. Fresh blades and instruments should be used with each new specimen as well as in different areas of the same specimen. Gloves and clean instruments should be used for resection and processing. To avoid desiccation and compromise of subsequent analyses, specimens should not be resected on a dry towel or other absorbent material.

Unless previously specified, tissue provided to the repository may be placed directly in appropriately labeled clean containers of cold biopreservation media (2 – 8°C) for transport to the repository for processing. If the tissue is to be frozen immediately, it is not necessary to place it in preservation media. Such media may cause ice crystals to form on the outside of the specimen when freezing. It is important to educate/train all personnel who will be handling the specimen on the specific handling requirements unique to each protocol.

Specimens requiring snap-freezing or flash freezing (cooling at sufficiently high rates to limit damage to cell structure from intracellular ice formation or prevent compositional changes in labile molecules) can be frozen in a *Dewar* of liquid nitrogen or on *dry ice* at the time of collection. Where specimen morphology but not viability of cells needs to be conserved, snap-freezing may be done in isopentane or isobutane pre-cooled with dry ice or with liquid nitrogen. Data should be maintained and tracked on the time that elapses between relevant time points (collection, processing, preservation, storage). A date and time stamp can be utilized for maintaining these records efficiently.

Referencing the associated diagnostic pathology report is not sufficient QC for surgical remnant clinical tissue aliquots collected by the *biorepository*. Because of tissue heterogeneity, QC for tissue specimens should be aliquot-specific with percentages of tumor, normal, necrosis, and/or fibrosis recorded using a pathologist's microscopic examination. This may be accomplished through hematoxylin and eosin (H&E) top-slide creation from FFPE and OCT-embedded tissues. Less resource-intensive

alternatives taking advantage of mirror-faces of tissue samples have been described[18]. Such alternatives offer both lower cost and the ability to know the composition of mirrored aliquots that are obtained without embedding, such as those snap frozen without additional media. All specimens should be labeled appropriately (Section I2.13. Labels) and all relevant accompanying data should be documented (Section I2. Inventory Systems). Specimen collection containers should be pre-labeled with barcode/donor ID for high-volume collections to improve workflow and ensure accurate labeling and specimen tracking.

Best Practice: All personnel who will be handling the specimen (*e.g.*, surgeons, nurses, pathologists, repository personnel) should be trained on the specific handling requirements of each protocol.

Best Practice: QC for surgical tissue samples should be aliquot-specific and performed prior to distribution.

K5.1.2. Post Mortem Collection (Autopsy/ Necropsy)

Remnant samples may be collected from *autopsy/necropsy* procedures consistent with relevant regulations. Requests for biospecimens should specify a maximum time interval post-mortem prior to processing. Autopsy/ necropsy procedures may yield "normal" tissues or large quantities of a specimen that would not otherwise be available from surgical procedures (*e.g.,* heart, brain). Specimens that are not removed as part of the routine autopsy procedure (*i.e.,* leg, arm, hand, foot, face tissue) are not usually available as their procurement may result in disfigurement of the body. There may be exceptions allowing procurement of such specimens if a specific consent has been obtained from a donor and/or the next of kin as appropriate under specific laws of the country or region of the acquisition.

Tissue specimens collected post-mortem should be appropriately labeled as to the organ site, tissue type, and time of resection, and then placed immediately into a container of cold biopreservation media (2 – 8°C) on wet ice. These organs can be dissected into smaller sections for processing and storage. Detailed information about the decedent should be recorded such as disease condition, age, sex, race, cause of death, time and date of death, and time of organ procurement. Information about the procured organ should include the condition (normal or diseased). Processing and storage of collected post-mortem specimens should be completed in a timely manner.

K5.1.3. Transplant

Occasionally, organs that are inappropriate for transplant may be offered or made available to a repository for research purposes. It is not unusual for the organ to have been out of the body for many hours beyond the normal time frame identified for procurement of samples. However, because transplant tissue is usually placed in a biopreservation medium at 2 – 8°C to maintain viability for transplant, most researchers will still accept transplant tissue as it is likely to be of superior quality to either surgical or autopsy specimens. Transplant organs may also be dissected into smaller sections during processing and storage. Information about the donor from whom the organ was procured should be obtained from the transplant center and recorded. All organs/tissues intended for research should be maintained in appropriate biopreservation media at 2 – 8°C until processed. Isotonic saline or culture media may not be considered optimal for hypothermic biopreservation of viable cells/tissues/organs. Specific perfusion techniques can be applied to organs, such as the liver, to enable isolation of specific cell types, such as hepatocytes.

In general, it is important to remove as much blood and other native fluids from the resected tissue/organ as soon as possible prior to processing. For larger or highly vascularized tissues in preservation solution, clot formation within the vasculature obstructs the penetration of the preservation solution into the tissue. This situation results in tissue specimens that are not homogeneously preserved and there could be localized tissue damage due to ischemia. Also, tissue damage could occur because ischemia and the clotting cascade impact the molecular profile of the tissue. These activities can produce changes in the molecular profiles of the

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tissue, resulting in the tissue section being less representative of its original resected state.

K5.2. Blood

One of the primary decisions in storing blood samples is whether to collect anticoagulated (*i.e.*, plasma, buffy coat, RBC) whole blood or coagulated (*i.e.*, serum, clot) blood. When serum is collected without anticoagulant, the blood clot obtained after processing can be used as a source of DNA for genotyping and other DNA-related studies[19]. In similar fashion, blood collected with anticoagulant can yield a packed cell volume (containing both the buffy coat and RBC) to be used as a source of RNA, DNA, or viable cells.

When multiple blood collection devices/containers are involved there is a prescribed priority order of draw (see Appendix A: Internet Resources). The order of draw for clinical testing may be different from an investigator's requested order of draw. The phlebotomist should follow the specified protocol and document the order of the draw. It is also important to determine which anticoagulants are acceptable for a particular downstream procedure (see Section K3.1 Specimen Stability).

Collection of blood samples may be done for many purposes. The collections should be done within a fit for purpose protocol with consideration of constraints of the collection (*e.g.*, geographic distance(s) between collection and processing site, low resource setting).

Blood collection and processing should take into consideration the required downstream experimental usage with special consideration of cellular, metabolic, and/or genomic analyses. These may require unique collection tubes, processing protocols, and storage conditions which need to be determined prior to blood collection.

Consideration should be given to the fact that cell viability and functionality of blood samples may be compromised during extended ambient storage/transport[20]. For DNA molecular analyses, new technologies have been developed to significantly extend ambient storage/transport of blood samples for up to 1 year[21]. Hypothermic temperatures (2 – 8°C) may allow for extended stability of certain blood-derived cell products (red blood cells).

Best Practice: Blood samples should be processed and stored within one to 24 hours of draw, depending on the analytical endpoints[22].

Best Practice: The protocol for a blood collection should be fit for purpose and considerations should be made for collection and transport constraints.

K5.2.1. Cord Blood

Arterial and venous cord blood can be obtained from delivered placentas after delivery and used for measuring blood gases or frozen and stored as a source of undifferentiated stem cells.

K5.3. Urine Specimens

Urine specimens should be maintained on wet ice or refrigerated after collection. Collection containers should be sterile and dry, have a 50-mL to 3-L capacity, a wide mouth, and a leak-proof cap. Depending upon the analyte to be measured, a preservative may be needed. The type of preservative may differ according to test methodologies, time delay, and transport conditions. EDTA, acidification, and sodium metabisulfite are examples of preservatives commonly used in urine collections. Urine containers used for environmental toxicology assays should be consistent with protocol requirements (*i.e.*, use of collection containers prescreened for phthalate metabolites).

Because urine may contain cellular and other elements, a urine sample is typically centrifuged to remove cells and debris. The acellular urine and separate cell pellet can then be analyzed and/or frozen as aliquots. A condensed urine on filter may be an alternative, cost-effective way of storing large-volume specimens. There are various methods of urine collection depending on the type of analysis intended. The collection method should be documented in the sample record.

K5.3.1 Urine Collection Time Parameters

K5.3.1.1.

First morning specimens are best for detecting substances in a more concentrated solution (*e.g.*, white and red blood cells, urinary hormones). The donor voids a urine specimen before going to sleep and collects the "first morning" urine immediately on rising.

K5.3.1.2.

Random collections are suitable for routine screening and cytology studies.

K5.3.1.3.

Fractional collections are used to compare the concentration of an analyte in urine with its concentration in blood. First morning urine, which contains solutes and metabolites from the evening meal, is discarded and a second urine sample following a period of fasting is collected.

K5.3.1.3.

Timed collections allow for comparisons of patterns of excretion of certain biomolecules. Typical collection times are 12 and 24-hour. For the 24-hour collection on day one, the donor empties his/her bladder and for the next 24 hours all subsequent urine is collected.

K5.3.2. Urine Flow Parameters

A midstream (clean-catch) can be conducted at any time of day or night. There is a reduced incidence of cellular and microbial contamination compared to the random sample because the donor is asked to clean his/her skin prior to collection and the urine is collected 'midstream', meaning the donor starts urinating and then positions the collection container in the stream of urine.

K5.4. Nail and Hair

Nail and hair clippings can be used for trace metal analysis to provide a longer-term measure of exposure. These samples are simple to collect, store, and ship. They can also be used as a source of DNA. Hair follicles may be collected and used for molecular analytes.

K5.5. Oral Specimens

Oral specimens can be used in a variety of assays. Collection devices for these specimens include swabs, washes, a non-covered cotton roll, a polypropylene-covered polyether roll, and can be combined with stimulation (*e.g.*, paraffin wax chewing stimulation).

K5.5.1.

Saliva may be collected for drug testing, HIV detection, monitoring of hormone levels, isolation of the microbiome, and as a source of DNA (buccal cells). It may be collected directly into a container with an opening large enough to facilitate this collection or mixed with mouthwash as the vehicle for collection. Saliva can be stored either as non-centrifuged aliquots or centrifuged, which results in supernatant and pellet aliquots which can then be analyzed and/or stored separately.

K5.5.2

Buccal cells may be useful as a source of DNA. A variety of collection techniques and containers have been developed specifically for these collections (see Appendix A: Internet Resources).

K5.5.3

Throat swabs and washes are collected primarily for research of Group A *Streptococcus* and *M. tuberculosis*.

K5.5.4

Nasopharyngeal swabs and washes are collected primarily for research of *B. pertussis* and respiratory viruses.

K5.6. Breast Milk Samples

Breast milk collection can be initiated when breast-feeding starts. Breast milk can be collected by manual expression or vacuum pump and should be collected in sterile or specially-cleaned bottles and is typically stored frozen. If certain analytes such as phthalates are of interest, the sample can be collected in a glass bottle and stored in the participant's household freezer.

K5.7. Stool Samples

Samples are self-collected by participant into a container that can be lined with plastic wrap or placed inside another container and then frozen. Some procedures will allow for lyophilizing the sample for long-term storage which provides a more inert (less odoriferous), smaller sample for analysis.

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Collection of stool samples in a stabilizer is the collection method of choice to avoid microbiome alterations taking place at room temperature and to minimize variability.

K5.8. Genital Specimens

Genital tract specimens are generally collected for the detection of sexually transmitted diseases such as *N. gonorrhoeae*, *Chlamydia trachomatis*, herpes simplex virus (HSV), human papillomavirus (HPV), agents of BV (bacterial vaginosis), Trichomonas, group B streptococci, and *Candida* species. Seminal fluid may be collected for semen analysis as part of fertility studies or post-vasectomy review.

K5.8.1. Female

Cervical screenings are routinely performed using liquid-based cytology in which the specimen is collected, normally by a small brush in a similar way as for a conventional smear test, but is deposited into a small bottle of preservative liquid rather than being transferred directly to a microscope slide. Cervical vaginal lavages (CVL) can be obtained and used for HPV and HSV studies[23,24]. CVL should be collected in one container and transported to the laboratory on wet ice within one hour of collection, vortexed gently, and aliquoted in a biosafety cabinet.

K5.8.2. Male

Collection of male genital specimens for bacterial or viral infections may be performed by urogenital swabbing, swabbing of lesions, or testing first morning urine specimens (see Section K5.3.1.1). Seminal fluid is collected in a warm (20 – 40◦C), clean, dry, wide-mouth container and should be delivered within an hour of collection if the collection takes place at a patient's home, but is preferably collected during a clinic visit in a private room.

K5.9 Miscellaneous Fluids

Other body fluids are collected for microbiological or clinical laboratory testing as part of diagnosis and management for a variety of diseases. Most (*e.g.*, pleural, peritoneal, pericardial) are collected by ultrasound-guided aspiration, while others, (*e.g.*, synovial fluid, amniotic fluid) collection employs visually-guided needle aspiration. Commonly collected body fluids include:

- Cerebrospinal fluid samples
- Synovial fluid
- Follicular fluid
- Serous fluids (*e.g.*, pleural, peritoneal, pericardial)

K6. SPECIMEN PROCESSING

Several online resources are available (see Appendix A: Internet Resources). Repositories should establish and follow their own Standard Operating Procedures (SOPs) or follow previously validated SOPs.

Some general considerations for specimen processing include:

- Safety precautions (see Section F6. Safety Topics)
- Inspection for accuracy of label, specimen deficiencies, etc.
- Maintaining specimen integrity (*i.e.*, stability, sterility, temperature)

For some downstream analyses, the presence or degree of non-conformities may be important and therefore should be recorded at the time of processing (*e.g.*, a minor non-conformity may be a volume under a specific amount and a major non-conformity may be the presence of hemolysis, lipemic (milky), or icteric/jaundiced (dark yellow) material). If any non-conformity or combination of non-conformities will result in specimen rejection, the rejection criteria should also be defined (*e.g.*, blood sample arrives with no label and identity cannot be determined) and the subsequent actions described (*e.g.*, specimen that meets the rejection criteria will be discarded) (see Section D4.3.3. Non-Conformities).

Best Practice: Non-conformities observed and subsequent actions taken during processing should be identified and documented.

Best Practice: When possible, two or more samples per specimen should be processed and stored for redundancy.

K7. RECEIVING SPECIMENS

SOPs should be in place for receiving specimens into the repository. All specimens provided to the repository from outside sources should be confirmed/verified and

a Verification Report maintained by the repository (see Section D5.3. Record Retention) and a copy provided to the site of origin. The report should document the following: receipt date and time, the shipment tracking number, package and container condition after visible inspection for signs of damage, confirmation of the condition of the coolant used during shipment, confirmation that specimens received match those listed on the Shipment Manifest sent with the shipment, and if number of containers match (if multiple are in the shipment) (see Section J4.2. Shipping Manifest and Tracking Number). If data loggers are enclosed in the shipper, they should be checked to determine if adverse temperature spikes have occurred. All discrepancies should be documented and reported immediately to the originating site. Both sites should attempt to resolve these discrepancies as soon as possible and the resolution documented in the Verification Report (see Section J4.3. Sample Receiving and Verification). These forms should identify the person recording the entries (name/signature/date).

Best Practice: Any problems encountered with a shipment should be communicated to the sender to aid in the prevention of similar problems in the future. Particular note should be made of the stability of the cold chain for specimens shipped in the chilled, vitrified, or frozen state.

K8. RETRIEVAL OF SPECIMENS FROM STORAGE

Retrieval of specimens for shipment or analysis requires strict adherence to protocols for proper specimen inventory and tracking, as well as adherence to established safety standards in working with freezers and other storage equipment.

K8.1. Locating Specimens in Storage

The location of specimens to be retrieved should first be verified in the appropriate specimen inventory system (Section I2. Inventory Systems). A requisition should be generated before specimens are retrieved from storage and retrieval should be performed following the repository's specimen requesting, tracking, and inventory protocols.

Best Practice: All requisitions should be checked against the inventory for accuracy before retrieval according to established SOPs and Quality Standards.

K8.2. Specimen Retrieval

Specimens should be located and pulled from storage as documented on specimen requisition forms. If specimens are frozen or vitrified, speed/efficiency is necessary during the retrieval process. Such speed may require that at least two individuals carry out the retrieval process. If possible, specimens being retrieved should be maintained at the storage temperature throughout the process (*e.g.,* specimens stored at -80°C should be kept on dry ice during the retrieval process). There are many commercial products available to maintain cold chain temperatures during retrieval. Forceps may be used when withdrawing specimens stored at liquid nitrogen temperatures to prevent warming of the specimens from body contact.

Once retrieved, staff should confirm that all requisitioned specimens have been included in the pull. Quality control checks should be performed to confirm that all specimens listed on the requisition were retrieved as well as the accuracy and integrity of their labels.

If specimens appear to be missing, the repository should have protocols to locate and/or document the missing specimens. Inventory systems should be updated to indicate missing and/or improperly located specimens and corrections made to specimen locations. To ensure collections are not depleted without careful consideration, mechanisms should be established to alert the repository when specimens being placed in a requisition to be pulled/used reach a defined, critical level. Depletion of remaining specimen(s) may require scientific and/or administrative approval (see Section M2.4. Review of Specimen Use Requests).

Best Practice: A second, independent quality control check should be performed to ensure that the correct specimens have been retrieved.

Best Practice: A policy should be in place regarding notification and actions to be taken when retrieval of specimens results in the remaining stock reaching a defined, critical level.

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K8.3. Thawing, Re-warming, and Aliquoting Specimens

K8.3.1. Liquid and Solid Tissue

If thawing of a frozen tissue specimen is required, this should be done using stipulated protocols relevant for the downstream uses of the specimen. If a water bath is used, care should be taken that surface moisture from water baths does not enter the sample containers. In the case of vitrified samples, optimization of re-warming is critical and it may be necessary to apply a two-phase and/or rapid re-warming process to ensure that the samples do not form ice crystals as they pass through the *Tg*.

Large-volume liquid samples (*e.g.,* sera, plasma, urine) may need to be processed into smaller aliquots for *distribution* to multiple end-users. Thawing before aliquoting may occur on wet ice or room temperature. The recommended protocol should be followed to maintain specimen integrity. The proper pipette and tip to use is determined by the required volumes and eventual analysis. If analyzing for persistent organic pollutants, using a plastic pipette and tip may contaminate the sample further. A different pipette tip should be used for each specimen.

An alternative to thawing a specimen for aliquoting is a drilling system that includes a motor that produces a sonic, linear oscillatory motion that removes a frozen biological sample from a stored frozen specimen without thawing the remainder of the specimen. However, the process can "burn" the edges of the specimen and, for liquid specimens, care should be taken that several aliquots are taken and combined since liquid samples may not be homogenous in their frozen state.

Best Practice: Specimen thawing method should be determined by the protocols of the end-user and downstream application.

Best Practice: Specimen containers should be opened and the specimens aliquoted in a *biological safety hood*, when sterility is critical. Sterile/clean vials and pipettes should be used to avoid contaminating samples.

K8.3.2. Viable Cells

The rate and method of freezing/thawing and cooling/rewarming specimens can have serious effects on the viability of cells. Specific freezing/thawing, vitrification, and cooling/re-warming protocols should be developed and validated, including the validation of appropriate biopreservation media (cryopreservation solution), devices, and cooling rate to ensure that the method used supports the known or anticipated use for the specimens (see Section K3.3. Biopreservation/Cryopreservation).

Although slow cooling is generally best to ensure cell viability in frozen specimens, the opposite process is required when thawing from the frozen state. Samples should be rapidly thawed for just enough time to thaw visible crystalline ice and so that sample temperature is still hypothermic (2 – 8°C). Cells should be quickly diluted in appropriate media to minimize toxicity from the cryoprotectant. Dilution protocols (which may include several washing steps in order to gradually dilute and wash out the cryoprotectant) should be optimized to circumvent damaging osmotic effects. In the case of vitrified specimens, optimizing cooling and re-warming regimens is critical for ensuring the formation and maintenance of a stable glassy state and preventing de-vitrification and ice nucleation during re-warming. Therefore, in contrast to controlled-rate freezing protocols, vitrification can involve rapid cooling and re-warming regimens.

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SECTION L: LEGAL AND ETHICAL ISSUES FOR BIOSPECIMENS

L1. GENERAL

The *collection*, storage, *distribution,* and *use* of biological materials in research raises many legal and ethical issues with repositories often serving as the intermediary between study participants and the scientific research community. On an international level, the collection and use of these materials is currently regulated by an amalgam of differing, and occasionally conflicting, laws and policies. Thus, repositories should proceed carefully, not only in their daily work, but also with respect to international exchange of *specimens* and associated data. Regulations in some countries address the ethical issues related to collections and use of specimens and to import and/or export of specimens as well as shipping regulations (see Section J: Packaging and Shipping). References and links to applicable regulations and guidelines are included in Appendix A: Internet Resources.

L2. COLLECTION OF HUMAN SPECIMENS

Key discussions of ethics in *human subject research* are found in a number of *documents* including the Declaration of Helsinki adopted by the World Medical Association in 1964 and revised several times subsequently, most recently in 2013. These issues are also discussed in the Belmont Report published by the U.S. Department of Health and Human Services in April 1979 (see Appendix A: Internet Resources). These documents include several fundamental key concepts:

- Freely-given *informed consent* is necessary before procurement of specimens and research on specimens may be conducted.
- Research should be well designed, be conducted by persons with appropriate expertise, and lead to meaningful conclusions.
- Every effort should be taken to reduce the risks to *subjects* and ensure that the risks do not exceed the benefit of the expected findings.
- Studies in animals should provide reason to believe that the study of humans is needed and is the only way to get the necessary information.

It is important to understand key terminology related to the legal and ethical issues for human specimens. Terms that describe whether and how specimens are linked to *donor* identity are often used in different ways and with different meanings in different contexts. Definitions of key terms have been included in the Glossary found in Appendix B.

The collection, storage, and use of human specimens and associated data should be conducted in a way that respects the subject and maintains privacy and confidentiality. In addition, repositories should adhere to and keep up-to-date on relevant national/federal human subject regulations, privacy regulations, and other relevant national/federal, regional, and local laws. Respecting individual privacy and confidentiality with respect to tissues and data must be considered in a context that includes risks and benefits to family members, community, and identified populations. This means that group risks and benefits cannot be ignored. For example, some regions prohibit the use of fetal tissues, embryos, or embryonic stem cells in biomedical research. Regulations that govern the collection and import and/or export of human specimens, including those mandated by the Convention on Biological Diversity, should also be observed.

L2.1. Human Subjects Review Board/Ethics Review Committee

A human subjects review board (*institutional review board* or *ethics review committee*) is any board, committee, or other group formally designated by an institution to review biomedical research involving humans, to approve the initiation of the research or of collections, and conduct periodic review of such research or collections. As a component of a human subjects/ethics review, the processes and procedures for collection, storage, distribution, and use of human specimens for research should be evaluated to ensure that these procedures are appropriate to protect human subjects. This review may include review of operating procedures and policies for obtaining informed consent and protecting the participant's privacy and confidentiality. The review may also include a review of repository governance and oversight systems and mechanisms for ensuring that use of specimens are for research that is scientifically and ethically sound (see Section A.2. Repository Governance). Data-sharing mandates should also be reviewed. In some countries, a National Ethics Body or a Central Ethical Committee may have the authority to approve the establishment and functioning of institutional repositories of human *samples* with the purpose of supporting health research.

L2.2. Informed Consent

Informed consent for the collection, retention, and use of specimens is a process that offers donors information sufficient to allow them to make an informed choice about whether to donate specimens and data to the *repository* and agree, where applicable, to future research use. Consent should only be obtained under circumstances that provide the prospective donor or the donor's representative sufficient opportunity to consider whether or not to donate and minimizes the possibility of coercion or undue influence. The information that is given to the donor or the representative should be understandable to the subject or their representative.

Types of consent include:

- Specific consent – obtained for a specific research project such that the details of the proposed use of the specimen(s) can be specifically outlined. Allows the use of biological specimens and related data only in immediate research and forbids any future study that is not foreseen at the time of the original consent.
- Broad consent – obtained for future research in which case general information regarding, or examples of, the possible future research uses are provided.
- Partially restricted consent – allows for the use of biological specimens and related data in specific immediate research and in future investigations directly or indirectly associated with them.
- Multi-layered consent (also termed tiered consent) – requires several options to be explained to the research subject in a detailed form.

Known restrictions on specimen use, including use in future studies, should be documented and associated with the specimen(s)/collection within the repository. A separate consent for research purposes other than those originally outlined may be required. In all conditions, the type of consent must be in accordance with applicable national/federal, regional, or local regulations and laws, as different jurisdictions may not permit the use of certain types of consents. The repository should have mechanisms in place to ensure that future research uses of specimens are consistent with the original consent (*e.g.,* through review by a human subjects/ethics review committee or other mechanisms consistent with applicable regulations, laws, and repository guidelines) (see Sections A3.1. Organizational Planning Considerations and Section M: Specimen Access, Utilization, and Disposition).

In some jurisdictions, regulations and laws may permit a human subjects or ethics review committee to waive informed consent for the use of human specimens for minimal risk research, provided certain conditions are met. Researchers should check with their human subjects or ethics review committee or other institutional officials to determine the permissibility and requirements of such a waiver.

Some regulations and laws may permit the use of an 'opting out' principle for human tissue leftovers from diagnostic sampling. After an obligatory information of potential donors, the consent for including the leftover material in a repository is presumed to be given, unless it is actively withdrawn by the donor.

Regulations regarding return of individual research results in some countries guarantee research participants access to information obtained through the use of their specimens. Other jurisdictions require that repositories have policies in place that describe how the discovery of serious and significant findings (defined as information that is uncovered either directly within the scope of the research or incidental to the research that has serious and significant health implications for the participant and/or their genetic relatives) should be handled. Thus, it is essential to perform a meaningful discussion regarding these issues with the human subjects/ethics review committee during the design of a repository protocol and informed consent, before attempting to return any research results to subjects, their families, or physicians.

Best Practice: An information sheet or brochure, describing the research, which may mention return of research results, should be distributed to participants when consent is sought.

L2.2.1. Withdrawal of Informed Consent

Participants should have the right to withdraw consent and to have their unused specimens and data removed from the repository unless the specimens and associated phenotypic or demographic data are *anonymous* and cannot be linked by the repository to donor identities. The conditions under which a donor may make this request as well as the logistics for how a

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donor initiates this request should be specifically outlined in the informed consent document. Any limitations on the withdrawal should also be described. For example, it may not be possible to retrieve specimens once they are anonymized or distributed and used for research.

Different types of withdrawal of consent include:

- No further contact with the donor of the specimen - continued retention and use of previously obtained specimens and information is permitted, as is access to information from health records.
- No further access - continued retention and use of specimens and information is permitted but no further access to information from health records is allowed.
- No further use of the specimen - no further contact with the donor is allowed, specimens and information are no longer available to researchers, no access to information from health records, and remaining specimens are to be destroyed.

Best Practice: Donor consent must be obtained unless waived by an authorized human subject/ethics committee constituted in accordance with applicable laws or regulations.

Best Practice: Repositories should have an ethically approved policy and/or procedure in place regarding the return of research results. The policy should define what (if any) results will be returned and to whom (*e.g.*, participant and/or genetic relatives), how participants would be contacted (if applicable), the process to be followed if re-contact is not possible, and whether or not support (*e.g.*, from a genetic counselor) would be provided.

Best Practice: The participant information sheet and consent form should address whether or not research results are expected to be returned. If research results may be returned, the consent form should explain the potential impacts the return of such findings may have on various issues such as income protection, insurance, employment, psychosocial coping, and family dynamics for the participant.

L2.3. Protection from Research Risks

Care should be taken to minimize the risks to subjects and ensure that risks do not outweigh the benefits of the expected findings from studies using the specimens. This includes minimizing physical risks and psychosocial risks associated with the collection and use of specimens and/or data. It is particularly important that the collection of specimens and data does not affect patient care.

The repository should follow well-documented procedures to protect the privacy and confidentiality of the donors from whom the specimens and/or data are obtained. Two examples of such approaches are *anonymization* and *de-linking* (or de-identifying).

Best Practice: The collection of specimens and/or data for research must never adversely affect patient care.

Best Practice: Every effort should be made to protect the privacy and confidentiality of data associated with the specimens.

Best Practice: Use of specimens should remain within the scope of permissible consent obtained.

L2.4. Specimens Obtained from Vulnerable Subjects

Extra care and attention should be given to the consent process when subjects are incapable of signing the consent form themselves.

L2.4.1. General

Vulnerable subjects may include those under heavy sedation, patients with dementia, or patients with syndromes of impaired consciousness such as coma, brain death, locked-in syndrome, and persistent vegetative state. Ethical guidelines for the management of patients in these conditions have been published by the British Medical Association (1996)[1] and the American Neurological Association Council on Ethical and Judicial Affairs (1999)[2]. In cases of demented or mentally incompetent donors, a relative or legally authorized representative could sign the consent form on the donor's behalf. In some countries, the donor must be informed regardless of their age, medical, or mental condition.

Best Practice: Special measures need be taken to obtain consent for use of specimens from subjects incapable of consenting themselves. Legally authorized representative's consent may be an option. Repositories should be well-versed with ELSI regulations when working on specimens from these subjects.

L2.4.2. Ethnic and Social Groups

At times ethnic and social groups or communities may be at risk due to the release of aggregate research findings even when no individually identifiable information has been revealed. In addition, some populations or groups have specific beliefs about the disposal and use of their specimens, which should be respected.

Best Practice: When research focuses on a particular community, it is best to seek input from representatives of the group on relevant aspects of the design of the study, the consent process, appropriate uses of specimens, and dissemination of collective research findings.

L2.4.3. Pediatric Subjects

The collection, storage, and distribution of specimens from pediatric subjects creates additional ethical considerations, particularly in the areas associated with the gathering of informed consent from subjects[3]. All elements associated with the use of samples from adult subjects should also be adhered to when working with pediatric subjects, including securing human subjects/ethics review board approval for all processes and procedures, the minimization of risk associated with subject participation including the risks associated with the loss of privacy and confidentiality, and the termination of specimen resources. The age of pediatric participants may be critical and require more detailed documentation (*e.g.*, days, months, years). Policies and legal requirements may differ by country and region.

L2.4.3.1. Parental Permission and Pediatric Assent

Subjects below a certain age (which may differ by region or country) are not able to provide informed consent. Instead, parental permission and pediatric subject *assent* (in cases where assent may be given) is obtained in lieu of informed consent. Assent should include helping the patient understand the nature of their condition, informing them of what they can expect with tests and treatment(s), and obtaining an expression of the patient's willingness to accept the proposed care[4] (see Appendix A: Internet Resources).

The documentation associated with obtaining parental permission is similar in nature and content to a document used to obtain informed consent from an adult with the exception that the documentation contains references to the minor child as the donor. The components of the parental permission documentation must include a complete and understandable description of the procedures associated with the collection, storage, and distribution of the specimens; risks and benefits (if any); options other than participating; and opportunities to withdraw permission. The process of securing parental permission should include the opportunity for the parent or guardian to discuss and question the pediatric donor's potential involvement in the research until a level of full understanding is reached.

Once parental permission is obtained, the process of securing pediatric assent may be undertaken if the donor in question is at an age and developmental level where assent may be given. The assent process should be conducted through the discussion of the research, procedures, and processes with the child in age-appropriate language, including the opportunity for the child to ask questions. As with the securing of parental permission, key topics must be covered with the child, including the facts that they do not have to participate and that they may withdraw their assent to participate at any time in the future. For children who are either not yet old enough to read or not able to read, this assent process may be conducted orally, assuming that the appropriate human subject/ethics committee has approved the enrollment of children of that age. For children of reading age and ability, a pediatric assent document should be utilized. Assent documentation should be drafted in language that is age appropriate, easily understood, and likely to encourage questions and discussion. As with the process to obtain informed consent and parental permission, the

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process associated with obtaining pediatric assent should be an interactive process where information is freely shared and decisions are made in an informed fashion.

L2.4.3.2. Age Considerations

Until the subject in question is of legal age, parental or guardian permission is required for the pediatric subject to participate in research. The question of when to progress from using a pediatric assent document to using an informed consent document is less clear and tends to be institution and/or human subject/ethics committee dependent. The process and documentation must be designed with the emotional, developmental, and cognitive abilities of the pediatric population in question. If the pediatric subjects are adolescents, it may be possible to use the same documentation as is used to secure informed consent from adult participants, with the caveat that parental permission is still required as a necessary first step. A new consent may be required from the participant once he/she reaches the age of majority.

L2.4.3.3. Withdrawal of Assent and/or Permission

Pediatric subjects and their parents or legal guardians must be informed that they are able to withdraw their assent or permission, respectively, at any point and decline to further participate in the process.

Best Practice: Appropriate parental permission and age-related assent, based on local regulations, should be obtained from pediatric subjects.

Best Practice: Repositories should consult with human subjects/ethics committee for guidance on whether subjects that have reached the age of majority should be re-consented or whether a waiver of informed consent by the human subjects/ethics committee is appropriate.

L2.5. Specimens Obtained from Autopsies

Specimens may also be obtained during *autopsy* from pathologists at hospitals, institutions, or the coroner's office. Full consent or authorization should be obtained from the deceased individual (*e.g.,* a signed agreement to donate their body for scientific research), the next of kin, or a legally authorized representative.

Repositories should follow relevant regulations pertaining to their particular jurisdiction.

L2.6. Specimens to be Used for Genetic Analyses

Complex ethical issues arise when genetic testing is performed on specimens. These issues include concerns about the potential identification of donors and risks to family members, particularly from whole genome-sequencing technologies. In addition, genetic analyses may raise complex questions such as whether to inform donors of their individual research results, whether to inform participants' families when heritable genetic factors about disease risks are identified in tissues, whether to ask relatives to collaborate on heritable genetic testing, and whether to advise relatives to seek genetic counseling.

Local requirements regarding use of specimens for genetic testing vary. In some jurisdictions, participants may consent only to some aspects of the research. In others, a separate consent form may be required when specimens are to be used for genetic testing or for germ line mutation analysis. Repositories should follow local regulations and laws regarding specific requirements for generating, using, and sharing genetic data.

Maintaining privacy of the participants and the confidentiality of their data is particularly important when genetic data are generated (see Section I: Repository Information Management Systems).

Best Practice: The repository procedures for collection, storage, distribution, use, and disposal of specimens should respect the perspectives and traditions of donors from whom the specimens were obtained and minimize the risks to communities, populations, and groups.

L2.7. Sharing and Distribution of Specimens and Data

Repositories should provide responsible custodianship of the specimens and data that they collect, maintain, and share. Mechanisms should be in place to maintain the quality of specimens and data, protect donor privacy, and confidentiality,

and to ensure that specimens are shared in a manner that is consistent with any consent obtained for them (see Section M2. Access and Utilization).

Specimens and/or data should only be made available for ethical and scientifically appropriate research that is expected to contribute to scientific discovery. Copyright and intellectual property in relation to sample metadata provided directly to researchers or presented on public websites should be accompanied by a policy that outlines the terms and conditions of its use.

L2.8. Ethical and Legal Disposal of Human Specimens

For some populations, disposal of specimens may have ethical considerations. Depending upon the nature of the study population and the repository, repositories and recipient researchers may be required to dispose of unused specimens according to local, legal, ethical, and *safety* rules for the disposal of human remains. Alternatively, recipient researchers may be requested to return unused specimens to the repository.

L3. COLLECTION OF NON-HUMAN BIOSPECIMENS

L3.1. Non-Human Organisms: Compliance with National Laws/Regulations and International Agreements

Collecting and carrying out certain types of research on wild organisms is controlled by international directives and national laws. Failure to heed these laws can be damaging for biodiversity, can circumvent fair access and benefit sharing among countries, and can create serious legal and operational problems for research organizations. International treaties set out requirements and advice on the rights and responsibilities of provider countries (the origin of a genetic resource/biological specimen) and users of that resource (including researchers and repositories). The relevant international agreements include the Convention on Biological Diversity (CBD) texts on Access and Benefit-Sharing (particularly the Bonn Guidelines and the Nagoya Protocol), the International Treaty on Plant Genetic Resources for Food and Agriculture, and the Cartagena Protocol on Biosafety. CITES permits are necessary for species covered under that convention. The special status of access and benefit sharing for genetic resources in food and agriculture has been discussed by the Food and Agriculture Organization of the United Nations. Each country, if it is party to any of these agreements, will have its own implementing legislation. For any sample collected there may be relevant legislation in the provider country, the collection's or researcher's own country, and any country through which the samples are carried.

In addition to permits relating to international agreements, other documents may be needed such as for collecting in protected areas, export and import permits, and phytosanitary/veterinary certificates. Some of these permits can take many months to obtain. Permits are often highly specific and attention should be paid to include the target sample derivative(s) (*e.g.*, whole specimen, viable cells, fixed tissue, DNA). For veterinary hospital patients, all processes and procedures for collection, storage, distribution, and use of specimens for research should receive prior approval from an IACUC board (U.S.) and collections should follow the same informed consent regulations listed above for human specimens, making sure the information is clear to the patient representative (owner). Broad consent and specific informed consent (for immediate research use) are most often used in veterinary hospital collections.

Best Practice: Legal and regulatory requirements of all relevant countries should be checked and necessary permits obtained during the collection planning process where possible.

L3.1.1. Access and Benefit Sharing

Many countries have national legislation and regulations, particularly with regard to access and benefit sharing. These may require that users or collectors of biological material:

- Obtain Prior Informed Consent (PIC) regarding their proposed utilization of the genetic resources within the material from the appropriate national and/or international bodies (*e.g.*, indigenous and local communities). This sets out an agreement regarding what will happen to the material after collection.
- Decide upon Mutually Agreed Terms (MAT) regarding sharing the monetary and/or

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non-monetary benefits arising from that utilization. Such agreements may be part of a Permit or Material Transfer Agreement or covered by a Memorandum of Understanding (MoU, also Memorandum of Cooperation). Several agreements may cover a single sample. Often little or no distinction is drawn between the genetic resources (*i.e.*, functional units of heredity) and the biological resources (*i.e.*, specimens) containing them.

The terms and conditions agreed to with PIC and MAT may persist and should be associated with the organisms when they enter collections or become subject to research.

Advice regarding requirements under access and benefit sharing legislation may be sought from the National Access and Benefit Sharing (ABS) focal point; contact details can be found on the ABS Clearing House. However, there may be additional regulations from different government departments of which the ABS Focal Point is unaware.

The benefits agreed to when the provider country gives approval to collect may be monetary (particularly if the utilization of the material has a commercial goal) or non-monetary, such as training and capacity building. Examples of both monetary and non-monetary benefits are listed in Appendix II of the Bonn Guidelines of the Secretariat of the Convention on Biological Diversity and the Annex of the Nagoya Protocol on Access and Benefit Sharing.

Good practice for academic institutions, including repositories, in the context of access and benefit sharing is set out in Biber-Klemm & Martinez (2016)[5]. Some consortia have also developed best practices and tools to assist in their implementation (*e.g.*, Consortium of European Taxonomic Facilities GGBN, Botanical Garden Conservation International). Code of Conduct documents sets out the basic principles to which the consortium adheres, and the Best Practices provide advice on how these principles might be implemented, and the policies and processes required. See Appendix A: Internet Resources for examples.

Increasingly, groups of organizations are combining to adopt common policies and standardized access and benefit sharing principles and agreements. For example, the Swiss National Academy of Sciences has produced a document that includes a sample access and benefit sharing agreement, as well as case studies and a Step-by-Step guide to compliance[6].

L3.1.1.1. Additional Information for Microorganisms

The Belgian Science Policy Office has produced the MOSAICC code of conduct (Micro-Organisms Sustainable use and Access regulation International Code of Conduct), the MOSAICS recommendations (a system for appropriate management of access to and transfer of microbiological resources), and TRUST (TRansparent User-friendly System of Transfer). TRUST is developed in cooperation with the World Data Centre for Microorganisms of the WFCC via the Global Catalogue of Microorganisms; it aims at managing the influence of CBD-compliant agreements on the scientific, technical, and administrative activities of culture collections and, more generally, incorporating the Nagoya Protocol into the daily life of microbiologists (see Appendix A: Internet Resources).

In addition to the above-mentioned documents, the Best Practice Manual on Access and Benefit Sharing issued by the Microbial Resource Research Infrastructure provides guidance for microbial biological resource centers on implementation of institutional ABS policies with regard to genetic resources and associated traditional knowledge. It suggests operating procedures for acquisition/accession and transfer of material as well as for other services. The document also aims at generally increasing transparency on how microbial resource centers conduct research on their holdings and utilize genetic resources and associated traditional knowledge. Access and Benefit Sharing is further discussed in Section M2.2. Benefit Sharing.

Best Practice: Repositories should follow national/federal, regional, local, and international guidelines related to Access and Benefit Sharing when planning to start collections.

L3.1.2. Responsibilities

Repositories should establish documented procedures and policies to ensure:

- The repository understands its rights and responsibilities under the appropriate treaties and relationships with providers.
- Its staff and associates abide by appropriate national laws /regulations and international agreements (*e.g.*, Nagoya Protocol).
- Material entering the repository is obtained with appropriate legal certainty and animals were collected in a manner consistent with pertinent guidelines (*e.g.*, IACUC).
- Material deposited in the repository can legally be retained and used as required.
- Terms and conditions (PIC, MAT, MTAs, permit(s), and MoUs) governing samples are managed effectively and complied with by the repository, including internal and external users of the repository.
- Terms and conditions (PIC, MAT, MTAs, permit(s), and MoUs) governing samples can be accessed effectively to manage use of those samples, including third-party transfer and disposal. This will include incorporation within a records management system and data management system.
- Third-party use of samples is carried out according to terms and conditions (PIC, MAT, MTAs, permit(s) and MoUs) governing those samples.
- Any proposed use outside the original terms and conditions (PIC, MAT, MTAs, permit(s), and MoUs) is renegotiated with the provider.

L3.2. Ethical Collection of Animal Specimens for Research

Scientific researchers who work with animal models generally agree that experiments that follow the best animal welfare procedures result in the best science. Three Rs (reduction, refinement, and replacement) in animal procedures should be an integral part of any research project to help minimize animal use and suffering and to facilitate good scientific practice.

The refinement of scientific procedures carried out on animals to minimize adverse effects and to maximize the scientific benefit gained is a legal and ethical requirement under the laws and regulations of numerous countries worldwide, including the U.S. Animal Welfare Act (United States Code, Title 7, Chapter 54, Sections 2131-2159), the U.K. Animals (Scientific Procedures) Act 1986, the U.K. Animal Welfare Act 2006, the Animal Health and Welfare Strategy for Great Britain, Australian Animal Welfare Strategy, Canadian Council on Animal Care in Science, among others. Nevertheless, refinements are not always implemented for a variety of reasons[7,8].

The 'five freedoms' concept first presented by the British Farm Animal Welfare Council (FAWC, 1979)[9] can be used as general indicators of laboratory animal welfare. These five freedoms are: (1) freedom from injury and disease; (2) freedom from discomfort, hunger, and thirst; (3) freedom from pain; (4) freedom to express normal behaviors; and (5) freedom from fear and distress. In any animal resources facility, researchers must implement actions to minimize the impact of the procedures they perform on these five freedoms.

Currently, animals are sacrificed in laboratories or breeding establishments for a variety of reasons including:

- When animals have passed the age of being suitable for breeding.
- To provide blood and other tissues samples for a scientific analysis.
- At the completion of an experiment or due to continuing adverse effects.
- To end an experiment because the levels of pain, distress, and suffering are likely to exceed a certain level.
- In situations where the health or welfare of the animals are a matter of concern.
- To eliminate animals with improper characteristics, such as type or sex.

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In terms of animal welfare, the primary criteria for euthanasia should follow these rules: the method should be painless; achieve rapid unconsciousness and death; require minimum restraint; avoid excitement; should be suitable for the age, species, and health of the animal; must minimize fear and psychological stress in the animal; should be reliable, reproducible, irreversible, and simple to administer (in small doses if possible); and safe for the operator. In the U.S., the IACUCs ensure that all projects involving the use of live vertebrate animals comply with federal regulations and guidelines and they review the appropriateness of euthanasia. IACUC uses The American Veterinarian Medical Association Guidelines for Euthanasia as criteria when reviewing euthanasia protocols, specifying appropriate methods and agents based upon published empirical evidence that demonstrates the minimization of pain and distress. Animal repositories in other countries should refer to their local regulations on animal euthanasia.

Through the harmonization of procedures among animal resource centers, it is expected that minimization/elimination of pre-analytical confounding variables and the resulting compatibility of studies will result in a reduced number of animals used for experimental research. Such harmonization will result in improved animal welfare standards in a way that both animals and science benefit from harmonization.

Best Practice: To ensure the ethical collection of animal specimens for research, repositories should refer to their local and national animal care and usage policy. Measures to minimize animal use, as well as pain and distress to them, in research should be undertaken where possible.

L3.3. Sharing and Distribution of Non-Human Specimens and Data

Repositories should provide responsible custodianship of the specimens and data that they collect, maintain, and share. Mechanisms should be in place to maintain the quality of specimens and data, protect the provider country rights, and ensure that specimens are shared in a manner that is consistent with legal and regulatory requirements (see Section L3.1. Non-Human Organisms: Compliance with National Laws/Regulations and International Agreements and Section M2. Access and Utilization). Some ABS agreements state that specimens may not be transferred to any third parties or may require written permission from the provider country for this to take place.

Specimens and/or data should only be made available for ethical and scientifically appropriate research that is expected to contribute to scientific discovery. Agreements with provider countries and others as a condition for access should be adhered to when considering third-party transfer and usage. A large number of Botanic Gardens have jointly created the International Plant Exchange Network, an organization that is legally one "person", which enables free movement of samples among its members while respecting ABS. Copyright and intellectual property in relation to samples metadata provided directly to researchers or presented on public websites should be accompanied by policy that outlines the terms and conditions of its use.

L3.4. Ethical and Legal Disposal of Non-Human Specimens

Disposal of non-human specimens may be governed by repository policy and also by agreements entered into with the provider country. These may be included in the original agreements governing collection and research.

L4. TERMINATION OF REPOSITORIES

Repositories should develop plans at the time of their establishment for the *disposition* of specimens and/or data should the repository be terminated for any reason. The disposition, including any transfer of specimens and/or data to third parties, should be consistent with the conditions and agreements under which specimens and/or data were obtained (see Section M3. Specimen or Collection Disposition).

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SECTION M: SPECIMEN ACCESS, UTILIZATION, AND DISPOSITION

M1. GENERAL

Repositories should establish written policies and procedures addressing how *specimens* and associated data will be accessed, what will constitute appropriate uses of the specimens preserved in the *repository*, and how decisions will be made to approve requests for specimens. Access and use of the *collections* should be included in the planning process and reflected in the governance of the repository.

Access to repository collections and associated data may be governed by legislation and regulations, which should be considered prior to release to the requestor especially if monetary benefits arise from their use (see also Section A2. Repository Governance)

Repositories should make their access and use policies available to sponsors and funding providers, *donors,* and, when appropriate, to the general public (see Section A2. Repository Governance) in order to create trust in the repository.

Best Practice: Repositories should establish written policies governing access and use of specimens and associated data and policies for *culling* and transfer of collections.

M2. ACCESS AND UTILIZATION

M2.1. Access and Use Policies

Repositories should develop policies governing sharing and *distribution* of specimens including guidance for determining what constitutes appropriate research use of the repository's specimens and associated data. The written policies that guide access and distribution should consider:

- Who can access the specimens and which specimens and associated data are available for sharing.
- Mechanism for submitting requests.
- Review process: who will review the requests and how decisions will be made.
- Criteria for determining whether a specimen request can be filled.
- Designated person or group providing oversight.
- Process for appealing requests that are rejected.
- Acknowledgement of repositories in publications and reporting requirements.

Restrictions on retention time of specimens in a repository and any restrictions on use of specimens (such as genetic research) specified in the Informed Consent *documents* for human subjects should be tracked and taken into consideration when distributing specimens.

Donor privacy and confidentiality should be protected at all times and specimens required for clinical care should not be made available for researcher use unless approved by an appropriate research ethics committee.

Those managing repositories storing genetic resources obtained from plants, animals, or microbes should be aware of any agreements made with providing countries that outline the utilization of *samples* for both non-commercial purposes (*e.g.*, taxonomy, conservation) and for commercial development (*e.g.*, pharmaceutical development, industrial biotechnology, commercial horticulture). Any proposed use outside the original terms and conditions must be renegotiated with the provider.

Best Practice: Access policies should be in compliance with existing rules, regulations, policies, and applicable laws.

Best Practice: Human specimens and associated data should be distributed without personal identifiable information unless this information is necessary and the human subjects or ethics committee review has granted permission for inclusion of identifying information.

Best Practice: Terms and conditions governing access and use of genetic resources obtained from plants, animals, or microbes should be tracked by the repository and taken into consideration when establishing access and use policies.

M2.2. Benefit Sharing

Sharing benefits from specimen research is important to ensure that providers of resources, especially those in developing countries, are treated in a fair and equitable way. The Nagoya Protocol, a supplementary agreement to the Convention on Biological Diversity (CBD), requires the fair and equitable sharing of benefits arising from the utilization of genetic resources and/or traditional

knowledge[1]. Users or collectors of biological material may be required to obtain Prior Informed Consent (PIC) and decide upon Mutually Agreed Terms (MAT) regarding sharing the monetary (*e.g.*, capacity-building, education, research partnerships, training) and/or non-monetary benefits (*e.g.*, access fees, commercial products, royalties, salaries). Depending on the Providing Country and domestic legislation, additional agreements with indigenous and local communities that hold rights on genetic resources need to be considered or may be required.

Benefits to participants in studies that collect human specimens, especially in developing countries, may include building local capabilities and infrastructure for biorepositories and research, creating research collaborations, and potentially improving the health of participating communities.

The repository policies should address ownership and benefiting from specimens, including intellectual property rights. Repositories supported with public funds should make their resources available to the wider community of researchers with due consideration to ethical and legal obligations.

Best Practice: Repositories that import specimens and data from other countries should ensure that fair and equitable benefits are made available to the providing country.

M2.3. Sharing Specimen/Sample Associated Data

Specimens/samples are most useful for scientific research when accompanied by specific data that characterize their key attributes and source to aid with the interpretation and analysis of experimental results. Data governance plans and policies should take into account:

- Type of data needed to accompany specimens from different human and/or non-human sources.
- Legal requirements related to data, protocols, consents, and other documents governing the repository.
- Material and data transfer agreements (Section M2.5.).

For human specimens, it is important to protect subject/donor identity and privacy, as described in detail in Section L. Whenever possible, human subject data should have all identifying information removed.

Quality control measures should be in place to ensure that the specimens are linked to the correct data.

Best Practice: Repositories should develop data sharing policies describing what type of specimen (or sample) associated data can be accessed and provided.

Best Practice: Repositories should develop policies for sharing specimen associated data consistent with applicable laws and regulations, including those related to transfer of intellectual property, informed consent, ethical and privacy standards, and formal agreements covering specific data sharing arrangements.

M2.3.1. Transfer of Specimen Associated Data

Specimens are most useful for scientific research when accompanied by specific data that characterize their key attributes and source to aid with the interpretation and analysis of the scientific user's experimental results. It is therefore important to ensure that specimens are linked to the correct corresponding data. The specimens associated data should be used in accordance with appropriate legal requirements including protocol, consent, and other documents governing the repository. For human specimens, it is important to protect subject/donor identity and privacy, as described in detail in Section L. Whenever possible, human subject data should have all identifying information removed.

Best Practice: Repositories should develop policies consistent with applicable laws and regulations, including those related to transfer of intellectual property, informed consent, ethical and privacy standards, and formal agreements covering specific data sharing arrangements.

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M.2.4. Review of Specimen Use Requests

Requests for specimen use should undergo some level of scientific and/or administrative review to ensure proper utilization.

Considerations may include:

- Scientific merit and potential impact of the proposed research.
- Whether the research use is appropriate to the nature and purpose of the repository.
- Availability of specimens of the specific type requested.
- Adequacy of the research design and benefits and risks of the proposed research.
- Legal and ethical considerations.
- Qualifications of the research team and research environment and funding to carry out the proposed research.

The level of review and administrative actions required may depend on the type of requests, such as requests for rare specimens and potential competition for their use, requests for large amounts of data, and those that require additional *processing*, pre-analysis, or special handling by the repository staff. Some repositories may have a cost recovery system for services associated with specimen distribution, as defined in the business plans of the repository (see Section H: Cost Management).

When investigators are required to obtain human subjects or ethics committee review and approval for the research use of specimens and/or data requested, documentation of such approval needs to be obtained prior to specimen or data distribution.

Repositories should establish transparent and efficient procedures and processes for review and distribution of specimen and data requests. Requests should be reviewed in a timely manner by qualified individuals.

Best Practice: A repository's policies and procedures for utilization of specimens and associated data should be consistent with all applicable institutional and national/federal legal and ethical requirements.

Best Practice: Repositories should train their staff on policies related to specimen access and use.

Best Practice: Repositories should have well-documented and clearly defined criteria for evaluating requests for access consistent with the repository's policies for specimen and data sharing.

M.2.5. Material and Data Transfer Agreements

M2.5.1. Material Transfer Agreement

A *Material Transfer Agreement* (MTA) is a contract that governs the transfer of tangible research materials between two organizations (a provider and a recipient) when the recipient intends to use it for his or her own (research) purposes. The MTA defines the rights of the provider and the recipient with respect to the materials and any derivatives. Biological materials such as specimens (including whole animals, plants, microorganisms), reagents, cell lines, plasmids, and vectors are the most frequently transferred materials, but MTAs may also be used for other types of materials, such as chemical compounds or software.

Other types of agreements without the title of MTA may be used but generally would serve the same purpose and have the same components as an MTA.

M2.5.2. MTA for Specimens

An MTA (or other document) for transfer of specimens to a recipient should address at a minimum:

- Purpose of the transfer.
- Restrictions on the use of the specimens (*e.g.*, specimens may not be banked, sold, used in other projects, redistributed to third parties).
- Requirements for maintaining privacy and confidentiality.
- Restrictions on re-identification (where de-identified specimens are provided).
- Requirements for appropriate *biosafety* knowledge for handling.
- Intellectual property rights.
- Publication/authorship rights and required acknowledgement of the repository providing specimens.
- Providing reports to the repository about specimen use and/results.

- Other factors that may govern the transfer (*e.g.*, indemnification, insurance, contractual requirements).

Best Practice: An MTA or similar agreement should be executed to document the obligations and responsibilities of parties involved in the transfer of materials from a repository prior to shipment. The agreement should be in place before the transfer occurs.

Best Practice: Repositories that receive or send material should have an MTA and maintain documentation for such transactions. Repositories should have templates of this document that can be used or modified as needed.

M2.5.3. MTDA or DTA for Specimen Data

Repositories should execute an agreement with recipients prior to data transfer. This agreement may constitute a stand-alone Data Transfer Agreement (DTA) or the necessary terms may be included in an MTDA (Material and Data Transfer Agreement). Content of such agreements may include:

- Description of the data to be distributed.
- Purpose for which the data will be used.
- Whether redistribution or forwarding of the data to others is permitted and under what circumstances.
- Protection of data against unauthorized access.
- Protection of donor privacy and confidentiality and re-identification (where de-identified specimens are provided).
- Custodianship, access, and control of transferred data.
- *Disposition* of data (destruction) upon research completion or agreement termination.
- Terms of agreement, indemnification, payment of fees, and rights and title to the research performed.
- Other factors that may govern the transfer (*i.e.*, contractual requirements, local considerations).

Best Practice: Repositories should execute an MTA that incorporates terms for data transfer or similar agreement with recipients who receive specimen-associated data from the repository.

M2.5.4. Requirements for Transfer of a Collection

A repository may have a need to transfer an entire collection to another repository or custodian. An MTA will need to be established to document allowable uses for the collection.

The transfer agreements should include sign-off by recipients to handle all specimens with the necessary safety methods and a statement that the providing repository is not liable for any health risk or damage that may result from the recipient's unsafe handling of the specimens. For more detailed information, see Section M3.3. Transfer of a Collection.

M2.6. Acknowledging Repositories and Reporting Utilization

In publications that result from the use of specimens, the repository should be acknowledged as the source of the specimens, preferably in the Material and Methods section (or in the acknowledgements) of a manuscript. Recommended format for repository citation can be found in Bravo et.al 2016[2].

Repositories may require users to provide reports on utilization of specimens provided and include the requirement in the MTA or MTDA (Section M2.5. Repositories may ask researchers to provide the repository with data derived from individual specimen or samples or aggregate research results.

Repositories may specify a date by which specimen recipients should provide data, taking into consideration any special requirements that some recipients may have to delay dissemination of results as specified in study protocols or to secure intellectual property rights.

Best Practice: Repositories supporting research should establish policies and procedures for acknowledgement in publications and for reporting requirements about the use of the specimens and the data provided by the repository. These requirements should be specified in the Material Transfer Agreements.

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M3. SPECIMEN OR COLLECTION DISPOSITION

Policies should be established for transfer or disposition of collections, specifying criteria and conditions and how decisions will be made and approved. Collections or specimens may be transferred out of the repository when specimen resources have fulfilled their original purpose, are no longer suitable for their intended purpose, or if participants no longer request the withdrawal of their specimens. Information about MTAs for transfer of collections is provided in Section M2.5.3. MTDA or DTA for Specimen Data.

M3.1. Culling

Culling of specimens or collections is the process of reviewing and eliminating selected specimens or entire collections from the repository either by destruction or transfer to a new *custodian*. Repositories should review their collections periodically and determine the need for their continued storage. This action may be needed periodically due to storage space constraints and/or the need to control costs. Other reasons may include consent issues, regulatory changes, and protocol modifications and/or compromised specimen integrity. Costs for *retrieval*, destruction, and/or transfer of specimens or collections should be considered and included in the repository budget plans.

Best Practice: Repositories should establish criteria for continued retention or disposition of specimens and collections that are included in repository policies.

Best Practice: Repositories should have documented procedures in place for regularly scheduled reviews of the inventory to ensure that specimens meet criteria for continued retention.

Best Practice: Repositories should document disposition of specimens or collections through destruction or transfer to a new custodian and retain the documents in the archival records of the repository.

M3.2. Specimen Destruction

There are a number of circumstances that may influence decisions to destroy an entire collection or specific specimens. Some of the reasons for destroying samples may include, for example:

- Specimen-associated information has been lost, the identity of the specimen(s) is not known, and potential risks and *biohazards* cannot be assessed.
- Specimen quality has been compromised by equipment failure or repeated freeze/thaw cycles that limit fit for research uses.
- When required by consent, study design, or regulation; when specimens in excess of the approved protocol were collected; when the status of a participant changes from "eligible to ineligible" or their case/control status changes; or when consent is withdrawn.
- Specimens have not been accessed or used or custodianship cannot be verified.

Repositories should include documentation about specimen destruction due to compromised quality in their quality management procedures. This information can be important indicators for areas needing improvement either in specimen handling or repository operations and risk management.

Safety precautions appropriate for the type of specimens and risk level need to be observed when specimens are destroyed. The repository should consider specific protocols (SOPs) to include methods to be used for destruction of all the specimen types stored in the repository.

Best Practice: Repositories should develop policies for destruction of specimens and collections, including the criteria and approvals needed.

Best Practice: A repository should document the destruction of any specimens, and monitoring specimen destruction due to compromised quality as part of quality management for the repository.

M3.3. Transfer of a Collection

When a repository needs to transfer an entire collection to another repository or custodian, an MTA will need to be established as described in Section M2.5.4. Requirements for Transfer of a Collection. Provisions should be made for transferring documentation associated with the collection to allow for an assessment of the risk level and biosafety requirements for handling the specimens, and to enable future uses of the specimens. The recipients must be advised of any known potential risks associated with the collections and of any consent and custodianship issues that may limit future use.

For human specimens, a research ethics review may be required by the institution accepting the new collection and for new uses for the specimens. For animal, environmental, and microbial specimens, any agreements or permits outlining access or benefit sharing must be transferred with the specimens. Transfer and future use of specimens must be in agreement with the details specified in these documents. The cost for retrieving and transporting the collection to the new custodian should also be taken into account (see Section H: Cost Management).

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APPENDIX A: INTERNET RESOURCES

These internet references are made available for information only. ISBER does not warrant any of the information contained therein.

SUBJECT	WEBSITE	ORGANIZATION/SOURCE	TOPICS
Access and Benefit Sharing (Genetic Resources)	http://abs.scnat.ch	Swiss National Academy of Sciences	The joint regulation of access to genetic resources and the sharing of benefits arising from their use by the researchers or companies from user countries and the representatives of the states, in which the genetic resources have been accessed
Access and Benefit Sharing (Genetic Resources)	https://www.cbd.int/	Convention on Biological Diversity	Bonn Guidelines and the Nagoya Protocol that address sharing the benefits from the utilization of genetic resources in a fair and equitable way
Access and Benefit Sharing (Plant Genetics)	http://www.fao.org/plant-treaty/en/	Food and Agriculture Organization of the United Nations	International Treaty on Plant Genetic Resources for Food and Agriculture addresses conservation and sustainable use of plant genetic resources
Access and Benefit Sharing (Biodiversity)	https://absch.cbd.int/	The Access and Benefit-sharing Clearing-house (ABSCH)	A platform for exchanging information on access benefit sharing and a key tool for facilitating the implementation of the Nagoya Protocol
Access and Benefit Sharing (Plants)	https://www.bgci.org/policy/policytools	Botanical Garden Conservation International (BGCI)	Policy development and implementation relating to plant conservation
Access and Benefit Sharing (Microorganisms)	http://bccm.belspo.be/projects/mosaicc	Belgian Science Policy Office	Micro-Organisms Sustainable use and Access regulation International (MOSAIC) Code of Conduct and recommendations
Access and Benefit Sharing (Microorganisms)	http://bccm.belspo.be/projects/trust	Belgian Coordinated Collections of Micro-organisms (BCCM)	TRUST (TRansparent User-friendly System of Transfer) of microbial material
Animal Welfare	http://homeoffice.gov.uk/science-research/animal-research/	Animal Health and Welfare Strategy for Great Britain, Home Office	The regulated use of animals for research in the development of drugs and medical technologies that help to reduce suffering among humans and animals
Best Practices (Biological Materials of Human Origin)	http://www.coe.int/t/dg3/healthbioethic/texts_and_documents/Rec_2006_4.pdf	Council of Europe Recommendation Rec (2006) 4 of the Committee of Ministers to member states on research on biological materials of human origin	Recommendations on the management of patient safety and prevention of adverse events in health care
Best Practices (Biological Resource Centers)	http://www.oecd.org/dataoecd/7/13/38777417.pdf	Organisation for Economic Co-Operation and Development	Consensus Best Practices for Biological Resource Centers in OECD Countries
Best Practices (Biological Resource Centers)	https://biospecimens.cancer.gov/bestpractices/2016-NCIBestPractices.pdf	National Cancer Institute; National Institutes of Health; U.S. Department of Health and Human Services	Best Practices for biospecimen handling, processing, storage and retrieval for specimens collected through NCI-sponsored research
Best Practices (Laboratory Medicine)	https://wwwn.cdc.gov/LabBestPractices/	The Centers for Disease Control and Prevention's (CDC) Division of Laboratory Systems (DLS)	Laboratory Medicine Best Practices provides recommendations on effective laboratory medicine practices
Best Practices (Access and Benefit Sharing of Biodiversity Collections)	https://www.cetaf.org/taxonomy/publications	Consortium of European Taxonomic Facilities (CETAF)	CETAF Code of Conduct & Best Practices for Access and Benefit-Sharing

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SUBJECT	WEBSITE	ORGANIZATION/SOURCE	TOPICS
Best Practices (Access and Benefit Sharing of Microorganisms)	http://www.mirri.org/fileadmin/mirri/media/Dokumente/generalDocs/MIRRI_ABS_Manual_web.pdf	Microbial Resource Research Infrastructure (MIRRI)	Best Practice Manual on Access and Benefit Sharing issued by the Microbial Resource Research Infrastructure (MIRRI)
Biodiversity Repository Registry	http://grbio.org/	Global Registry of Biodiversity Repositories	Clearinghouse of information about biological collections in natural history museums, herbaria, and other biorepositories
Bioethics	https://www.aap.org/en-us/about-the-aap/Committees-Councils-Sections/Section-on-Bioethics/Pages/Bioethics.aspx	American Academy of Pediatrics Committee on Bioethics	Policies on bioethics in pediatric clinical care
Bioethics	http://bioethics-international.org/iab-2.0/index.php?show=objectives	International Organisation of Bioethics	The IAB facilitates the exchange of information between those working in bioethics in different parts of the world
Bioethics Advisory Committee	http://www.bioethics-singapore.org/	Bioethics Advisory Committee, Singapore	Resources for the ethical, legal, and social issues arising from biomedical sciences research in Singapore
Biorepository Protocols	http://www.abrn.net/protocols.htm	Australasian Biospecimen Network	Protocols and best practices for collecting and processing human biospecimens
Biosafety	http://governance.iarc.fr/ENG/Docs/safetymanual.pdf	The Division of Biosafety and Biotechnology (SBB), Scientific Institute of Public Health in Belgium	Biosafety risk assessment tools and Biosafety manuals, laws and regulations, guidelines on containment facilities, equipment and practices, shipping and transport
Biosafety	http://www.ebsaweb.eu/Resources.html	European Biosafety Association	Conferences and other resources on European biosafety issues
Biosafety	http://www.ebsaweb.eu/ebsa_media/Downloads/Biosafety7-view_image-1-called_by-ebsa.pdf	World Health Organisation	Laboratory biosafety manual covering equipment and facility design and techniques
Biosafety	https://www.canada.ca/en/public-health/services/laboratory-biosafety-biosecurity/pathogen-safety-data-sheets-risk-assessment.html	Public Health Agency of Canada (PHAC)	Pathogen Safety Data Sheets (PSDSs) that describe hazardous properties of a human pathogen and provide recommendations for work involving these agents in a laboratory setting
Biosafety	http://www.cjd.ed.ac.uk	UK Surveillance Unit for Creutzfeldt-Jakob Disease	Surveillance data on Creutzfeldt-Jakob Disease; technical information; links
Biosafety	http://bch.cbd.int/protocol	Convention on Biological Diversity	Cartagena Protocol on Biosafety is an international agreement on the safe handling, transport, and use of living modified organisms resulting from modern biotechnology that may have adverse effects on biological diversity
Biospecimen Stability Calculator Tool	http://www.isber.org/?page=STABCALC	Biospecimen Stability Testing Calculator Tool (STABCALC)	Standardized tool to perform stability studies and examine biomarker stability
Blood Collection Protocols	http://www.csmc.edu/5455.html	Cedars-Sinai Medical Center	Blood collection guidelines
Convention on Biological Diversity	http://www.cbd.int	United Nations Environmental Programme	Sustainable development and Intellectual Property Rights
Convention on International Trade in Endangered Species of Wild Fauna and Flora	http://www.cites.org	IUCN (The World Conservation Union)	Trade in Endangered Species of Wild Fauna and Flora
Case Studies of Human Tissue Repositories	http://www.rand.org/pubs/monographs/2004/RAND_MG120.pdf	Rand Corporation and the National Cancer Institute	Best Practices for repositories based on information collected from a defined number of U.S.-based repositories

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SUBJECT	WEBSITE	ORGANIZATION/SOURCE	TOPICS
Chemical Safety	http://www.cdc.gov/niosh/database.html	National Institute for Occupational Safety and Health (NIOSH), U.S.	Databases and information resource links and publications in the United States
Chemical Safety	http://www.ilo.org/public/english/protection/safework/cis/products/icsc/dtasht/index.htm	International Occupational Safety and Health Information Center	Chemical database; International Chemical Safety Cards (ICSC)
Chemical Safety	http://www.cdc.gov/niosh/chem-inx.html	Master Index of Occupational Health Guidelines for Chemical Hazards (NIOSH), U.S.	U.S. National guidelines for chemical hazards of specific chemicals
Chemical Safety	http://www.who.int/ifcs/en/	Intergovernmental Forum for Global Chemical Safety	Policy guidance on chemical safety
Chemicals Management	http://www.environment.gov.au/settlements/chemicals/index.html	The Australian Government Department of the Environment and Water Resources	Chemicals management strategies to protect human health and the environment
Classification and Labelling of Chemicals	http://www.unece.org/trans/danger/publi/ghs/ghs_rev00/00files_e.html	Globally Harmonized System of Classification and Labelling of Chemicals (GHS)	Contains harmonized classification criteria and hazard communication elements
Cost Modeling	https://biospecimens.cancer.gov/resources/bemt.asp	Biorepositories and Biospecimen Research Branch, National Cancer Institute, U.S. Department of Health & Human Services	Biobank economics modeling tool (BEMT) - a publicly available web-based financial planning tool for biobanks. BEMT is designed to enhance the understanding of the economic considerations involved in initiating, operating and maintaining a biobank to assist with long term financial planning and cost recovery.
Cost of User Fees	https://biobanking.org/webs/biobankcosting	Biobank Resource Center – University of British Columbia	A comprehensive and easy to use tool that captures annual expenses, resources, and biospecimen accrual and calculates the appropriate user fees
Calculation and Recovery of Costs	http://stm.sciencemag.org/content/6/261/261fs45	Science Translational Medicine 05 Nov 2014: Vol. 6, Issue 261, pp. 261fs45 DOI: 10.1126/scitranslmed.3010444	A calculation grid developed by an international expert group was tested across biobanks in six countries to evaluate costs for collections of various types of biospecimens
Cost Calculator	https://epi.helmholtz-muenchen.de/tools/calc/	Biobanking and Biomolecular Resources Research Infrastructure – Large Prospective Cohorts (BBMRI)	Tool that enables biobanks to calculate their biobanking associated costs and to determine a price strategy for samples, data, and services; designed for population based cohorts and biobanking in clinical studies
Disinfection and Sterilization	https://www.cdc.gov/infectioncontrol/guidelines/disinfection/index.html	Centers for Disease Control and Prevention, U.S. Department of Health & Human Services	Guideline for Disinfection and Sterilization in Healthcare Facilities (2008) presents evidence-based recommendations on preferred methods for cleaning, disinfection and sterilization of patient-care medical devices and for cleaning and disinfecting the healthcare environment
Dry Ice Safety	http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32008R1272:EN:NOT.	Regulation (EC) No 1272/2008 of the European Parliament	European regulations for dry ice
Dry Ice Safety	http://www.ercweb.com/resources/viewreg.aspx?id=6779	Environmental Resource Center	Requirements for shipping dry ice
Electrical Safety	http://www.ehs.uconn.edu/Word%20Docs/Electrical%20Safety%20in%20the%20Lab.pdf	University of Connecticut Environmental Health and Safety	Electrical safety in the laboratory

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SUBJECT	WEBSITE	ORGANIZATION/SOURCE	TOPICS
Environmental Health	http://www.environment.gov.au/approvals/index.html	The Australian Government Dept. of the Environment and Water Resources	Approvals, permits, and licensing
Environmental Specimen Bank Design	http://www.ehponline.org/members/1995/Suppl-3/wise-full.html	U.S. National Institute of Standards and Technology	Paper presented at the Conference on Human Tissue Monitoring and Specimen Banking: Opportunities for Exposure Assessment, Risk Assessment, and Epidemiologic Research held 30 Mar-1 Apr,1993 in Research Triangle Park, ,NC
Ethics Committee	http://www.hugo-international.org/committee_ethics.htm	Human Genome Organisation	Promotes discussion and understanding of social, legal and ethical issues as they relate to the conduct of, and the use of knowledge derived from, human genome research
Ethics Guides	http://www.moh.govt.nz/moh.govt.nz/moh.nsf/indexmh/guidelines-use-human-tissue	New Zealand Ministry of Health	Guidelines for the Use of Human Tissue for Future Unspecified Research Purposes
Exposure Prevention Program Information	http://www.healthsystem.virginia.edu/internet/epinet/subpage2.cfm	Exposure Prevention Information Network; University of Virginia, International Health Care Worker Safety Center	Provides standardized methods for recording and tracking percutaneous injuries and blood and body fluid contacts
General Safety	http://www.osha.gov/comp-links.html	Occupational Safety and Health Administration, Department of Labor, USA	Current U.S regulations and regulations under development; technical, prevention and training information; links
General Safety	http://www.lbl.gov/ehs/pub3000	Lawrence Berkeley National Laboratory; University of California, California, U.S.	U.S.-based health and safety manual
Human Subjects	https://wcd.coe.int/ViewDoc.jsp?id=977859	Council of Europe; Committee of Ministers	Recommendation Rec(2006)4 of the Committee of Ministers to member states on research on biological materials of human origin
Human Subjects	http://www.hhs.gov/ohrp/international/HSPCompilation.pdf	Office of Human Research Protections; U.S. Department of Health and Human Services	Human subjects research legislation, regulations, or guidelines for 79 countries, two confederations and two organizations
Human Subjects	http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm	Office of Human Research Protections, U.S. Department of Health and Human Services	U.S. Federal Human Subjects Regulations
Human Subjects	http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm	Food and Drug Administration, U.S. Department of Health and Human Services	U.S.-based human subjects regulations: 21 CFR parts 50, 56, 812
Human Subjects	http://www.hhs.gov/ohrp/policy/index.html	Office of Human Research Protections, U.S. Department of Health and Human Services	Policy documents from the Office of Human Research Protections, U.S.
Human Subjects	http://www.hhs.gov/ohrp/international/	U.S. Office of Human Research Protections, U.S. Department of Health and Human Services	International Compilation of Human Subjects Research Protections
International Statistical Classification of Diseases and Related Health Problems	http://apps.who.int/classifications/apps/icd/icd10online/	World Health Organization (WHO)	The international standard diagnostic tool for epidemiology, health management, and clinical purposes

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SUBJECT	WEBSITE	ORGANIZATION/SOURCE	TOPICS
Inventory System Evaluation	http://www.isber.org/resource/collection/b1088675-1b3c-414c-b280-fb84327d3675/ISBERInformationSystemEvaluationChecklist.xlsx?hhSearchTerms	International Society for Biological and Environmental Repositories	Checklist to assist in the selection of a repository inventory management system
Laboratory Automation	http://www.slas.org/	Society for Laboratory Automation and Screening	Laboratory automation including liquid handling, sample storage and retrieval, specimen processing
Laboratory Design	https://www.orf.od.nih.gov/PoliciesAndGuidelines/BiomedicalandAnimalResearchFacilitiesDesignPoliciesandGuidelines/Pages/policy-index.aspx	NIH Office of Research Facilities	The NIH Design Policy and Guidelines establishes policy, design standards, and technical criteria for use in programming, designing, and constructing new buildings, and major and minor alterations for the NIH
Laboratory Standards Development	http://www.clsi.org	Clinical and Laboratory Standards Institute	U.S.-based general and technical information for the development of laboratory standards
Microorganism and Culture Collection Resources	http://www.wfcc.info/home/	World Federation for Culture Collections (WFCC)	Collection, authentication, maintenance, and distribution of microorganisms and cultured cells
Natural History Museum Benefit Sharing Practices	http://www.canmexworkshop.com/documents/papers/III.5d.2.pdf	International Expert Workshop on Access to Genetic Resources and Benefit Sharing	Concepts in Benefit Sharing for Museum Collections
Nomenclature Standards (human)	https://www.snomed.org/	SNOMED International	Provides global standards for health terminology
Nomenclature Standards (veterinary)	http://venomcoding.org/VeNom/Welcome.html	Veterinary Nomenclature (VeNom)	A list of standardized terms used in veterinary practice
Nomenclature Standards (biodiversity)	https://terms.tdwg.org/wiki/GGBN_Data_Standard	The Global Genome Biodiversity Network (GGBN) Data Standard	A set of vocabularies designed to represent tissue, DNA, or RNA samples associated to voucher specimens, tissue samples, and collections
Occupational Health and Safety	http://governance.iarc.fr/ENG/Docs/safetymanual.pdf	International Agency for Research on Cancer	Health and safety manual
Occupational Health and Safety	http://www.ccohs.ca/	Canadian Centre for Occupational Health and Safety	Information on biological hazards, chemical and materials, health and safety programs
Packing and Shipping	http://www.iata.org/index.htm	International Air Transport Association (IATA)	Standards for shipping human specimens by air
Packing and Shipping	http://www.icao.int/	International Civil Aviation Organization (ICAO)	International Transport Regulations
Packing and Shipping	http://hazmat.dot.gov/hazhome.htm	U.S. Department of Transportation (DOT)	U.S.-based standards for shipping human specimens by ground
Plant Collection Protocols	http://www.uaf.edu/museum/herb/howtocoll.html	University of Alaska, U.S.	Guidance on collecting plant specimens
Privacy	http://www.hhs.gov/ocr/hipaa/	U.S. Department of Health and Human Services	Health Insurance Portability and Accountability Act of 1996 (HIPAA)
Privacy	http://privacyruleandresearch.nih.gov/	National Institutes of Health, U.S. Department of Health and Human Services	HIPAA Privacy Rule and research
Privacy	http://www.usdoj.gov/oip/04_7_1.html	U.S. Department of Justice	Privacy Act of 1974, 5 U.S.C. § 552a
Radiological Safety	http://www.jmu.edu/safetyplan/radiology/advisorycommittee.shtml	James Madison University	Example of U.S. radiation protection program

SUBJECT	WEBSITE	ORGANIZATION/SOURCE	TOPICS
Records Management	https://oma.od.nih.gov/DMS/Pages/Records-Management.aspx	National Institutes of Health, U.S. Department of Health and Human Services	Program responsible for planning, controlling, directing, organizing, training, promoting, and conducting other managerial activities involved with respect to records creation, records maintenance and use, and records disposition
Resources for Pathology Laboratories	http://www.cap.org/apps/cap.portal?_nfpb=true&_pageLabel=reference	College of American Pathologists	General and Technical Information for lab management for U.S.-based laboratories
Specimen Tracking	http://www.leicabiosystems.com/pathologyleaders/specimen-tracking-helping-prevent-misdiagnosis/	Leica Biosystems	Guidance on specimen labeling and tracking
Standards	http://www.aabb.org/sa/Pages/default.aspx	American Association of Blood Banks (AABB)	Standards for blood banks and transfusion services, cellular therapies, perioperative services, relationship testing, immunohematology reference laboratories, molecular testing, and patient blood management
Standards	https://clsi.org/	Clinical & Laboratory Standards Institute (CLSI)	Consensus-based medical laboratory standards
Standards	https://www.cen.eu/Pages/default.aspx	European Committee for Standardization (CEN, French: Comité Européen de Normalisation)	Responsible for developing and defining voluntary standards at European level
Standards	http://publications.iarc.fr/Book-And-Report-Series/Iarc-Technical-Publications/Common-Minimum-Technical-Standards-And-Protocols-For-Biobanks-Dedicated-To-Cancer-Research-2017	Common Minimum Technical Standards and Protocols for Biobanks Dedicated to Cancer Research	Guidelines and recommendations for biobanks based on validated and/or evidence-based guidelines
Temperature Mapping of Storage Areas	http://www.who.int/biologicals/expert_committee/Supplement-8-TS-mapping-storage-areas-ECSPP-ECBS.pdf	World Health Organization	Guidance for the storage and transport of time and temperature-sensitive pharmaceutical products
Tissue Procurement Protocols	http://www.tubafrost.org	European Human Frozen Tumour Tissue Bank (TuBaFrost) project	Collection and storage of human tissues
Tissue Procurement Protocols	http://www.bd.com/vacutainer/pdfs/plus_plastic_tubes_wallchart_orderofdraw_VS5729.pdf	Becton-Dickinson	Wall chart on blood tube order for blood collection
Transnational Shipment of Chemicals	http://www.basel.int/	The Basel Convention	Transnational boundary movements of hazardous wastes and their disposal
Transport of Infectious Substances	http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_CSR_LYO_2004_9Final.pdf	World Health Organization	Recommendations developed by the United Nations Economic and Social Council's Committee of Experts on the transport of dangerous goods
Transportation Safety	http://www.cta-otc.gc.ca/legislation/index_e.html	Canadian Transportation Agency	Transportation-related legislation and other related matters can be found here, along with details of the Statutes and Regulations enforced by the Canadian Transportation Agency
Wildlife Trade Regulations	http://ec.europa.eu/environment/cites/legis_wildlife_en.htm	European Council Regulation No. 338/97	Regulations on the protection of species of wild fauna and flora by regulating trade and to suspend the introduction into the community of certain species from certain countries

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APPENDIX B: GLOSSARY

Unless otherwise defined in another context in these Practices, important terms are defined below.

ALIQUOT (Aliquoted, Aliquoting) – A process wherein a specimen is divided into separate parts which are typically stored in separate containers as individual samples. The term aliquot may also be used as a noun to denote a single sample.

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.

ANNOTATION – Additional information associated with a particular point in a document or other piece of information.

ANONYMIZATION – Involves completely removing all identifying information from specimens and data, eliminating the possibility of re-identifying the participant or re-contacting donors. This also precludes any return of research results, possibility for donor withdrawal, and limits the use of the specimens in future research.

ANONYMOUS – Identifiable personal information was not collected for the specimens and associated data or, if collected, was not maintained and cannot be retrieved, such that there is no way to trace the identity of the subject from whom the specimens were obtained.

ASSENT – To agree, as to a proposal; concur.

AUDIT – A documented review of procedures, records, personnel functions, equipment materials, facilities, and/or vendors in order to evaluate adherence to written SOPs or government laws and regulations.

AUTOPSY – Postmortem examination of the organs and tissues of a body to determine cause of death or pathological conditions.

AXENIC STATE – State of non-contamination by or non-association with any other living organisms.

BANKING – The process of storing material or specimens for future use (see also *BIOBANKING*).

BIOBANK – See *REPOSITORY.*

BIODIVERSITY BIOBANK – A biobank holding molecular-level biodiversity samples (e.g., from animals, plants, fungi, microorganisms; also includes many types of environmental samples).

BIOHAZARD – An organism, or substance derived from an organism that poses a threat to (primarily) human health. This can include medical waste, samples of a microorganism, virus, or toxin (from a biological source) that can impact human health. It can also include substances harmful to animals.

BIOLOGICAL SAFETY CABINET (BIOSAFETY CABINET, BIOSAFETY HOOD) – Cabinet designed to provide microbe-free work free work environment which enables workers to perform work on samples in an isolated area.

BIOREPOSITORY – See *REPOSITORY.*

BIOSAFETY – The discipline addressing the safe handling and containment of infectious microorganisms and hazardous biological materials to prevent harm to workers, non-laboratory organisms, or the environment through the application of containment principles and risk assessment.

BIOSPECIMEN RESOURCE – A collection of biological specimens that is acquired for a defined purpose. Management responsibility of the biospecimen resource is led by the custodian for the collection. Biospecimen resources may be stored in a repository or laboratory, depending on the numbers of specimens contained therein.

CALIBRATION – The process of adjusting the output or indication on a measurement instrument to agree with value of the applied standard, within a specified accuracy.

CHAIN OF CUSTODY – Refers to the chronological documentation or paper trail showing the full process of acquisition, transfer, handling, and disposition of physical or electronic materials.

COLD CHAIN – A temperature-controlled supply chain.

COLD ISCHEMIA – The time a tissue or organ is chilled during decreased blood perfusion or after the blood supply has been reduced or cut off.

COLLECTION – May refer to the practice or technique of collecting a specimen (See *RETRIEVAL*) or to a specific sample or group of samples that has been isolated for future research purposes.

CONTAINER – 1. An object that can be used to hold or transport something. 2. Enclosure for one unit or more units of specimen(s).

CRYOPROTECTANT – An additive or mixture of additives that allow living cells, tissues, organs, and organisms to survive exposure to cryogenic temperatures, of which the main type is a colligative cryoprotectant. This is a protective additive that must be able to penetrate the cell, applied to prevent damage caused by excessive cell volume changes and the toxic concentration of solutes (i.e., colligative injury). An osmotic cryoprotectant is an additive that does not penetrate the cell. It confers additional protection by osmotically withdrawing water from the cell (osmotic dehydration), consequently reducing the amount of water that is available to form ice. Mixtures of colligative and osmotic cryoprotectants are often used in plant, algal, and microbial cryoprotective solutions, as well as in cryoprotective solutions for some mammalian cells.

CULLING – Reviewing and eliminating specimens in a collection or an entire collection either by destruction or transfer to a new custodian.

CUSTODIAN – The individual responsible for the management of a biospecimen resource. The custodian works with other key stakeholders in the management of the resource including the tracking of all relevant documentation for the resource and for ensuring that policies regarding access to the resource are in place and implemented according to appropriate guidelines.

DATABASE – A structured collection of records or data that is stored in a computer system so that a computer program or person using a query language can consult it to answer queries.

DEHYDRATION – Removal of water from a tissue.

DE-LINKING – Involves the use of unique code(s) to link specimens and data to donors. The repository or a third-party intermediary may act as an "honest broker" and hold the link between the codes and donor specimens and data. Researchers, receiving the specimens, receive the coded specimen(s). Regulations regarding de-identification may vary in different areas and investigators are encouraged to review local, state, and national/federal regulations and laws. (Also known as *DE-IDENTIFYING*.)

DESICCATION – Excessive loss of moisture; the process of drying up.

DEVIATION – An intentional or unintentional event that is a departure from a procedure or a normal practice.

DEWAR – A specialized container to hold liquefied gases. A Dewar may also be referred to as a Dewar flask or Dewar vessel.

DISINFECTANT – An agent that reduces the number of viable microorganisms.

DISPOSITION – Final destination of specimens.

DISTRIBUTION – A process that includes receipt of request for specimens, selection of appropriate specimens, and final inspection, in conjunction with subsequent shipment and delivery of specimens to another repository, specimen collection center, or laboratory.

DOCUMENT n. – A piece of written, printed, or electronic matter that provides information or evidence or that may serve as an official record. v. - Record, register, report (something) in written, photographic, or other form.

DONOR – Living or deceased individual who is the source of the specimen in accordance with established medical criteria, procedures and privacy regulations. In some countries the term SUBJECT or "individual" may be used in the same context as donor, especially as the context relates to human specimens.

DRY ICE – Solid phase carbon dioxide (CO2). CO2 solidifies at -78.5◦C.

END-USER – A health care practitioner, scientist, or laboratory staff member who performs an appropriate procedure, test or archival function.

ENVIRONMENTAL MONITORING SYSTEM – An automated, centralized monitoring system that monitors environmental conditions and alarms in conjunction with remote access, security features, and electronic data storage.

ENVIRONMENTAL SPECIMEN BANKS (ESBS) – Collect, preserve, and manage environmental samples (e.g., leaves, soil, water, animal or human tissue and fluid, ice cores, etc.), derivatives and associated data through standardized protocols. Samples are obtained through monitoring projects and surveys in order to support research, document environmental change, and/or to assess the effectivity of or necessity for regulatory acts.

ERGONOMICS – The science that explores human abilities and limitations, and applies that knowledge to improve a person's interactions with their environment, tools, products, and practice.

ETHICS REVIEW COMMITTEE – See *INSTITUTIONAL REVIEW BOARD.*

FEDERATED COLLECTIONS – Created when specimens are collected, processed, and stored at physically separated sites that each function as the specimen custodian for its local collection while related data is managed through a central database.

FIT FOR PURPOSE (var. – *FITNESS FOR PURPOSE*) – Suitable; appropriate, of a necessary standard, for its intended use.

FREEZE-DRIED – Dehydrated for storage by conversion of the water content of a frozen specimen to a gaseous state under vacuum. Also called lyophilized.

GLASS TRANSITION – The temperature at which a polymer transitions from a hard, glassy material to a soft, rubbery material.

HUMAN SUBJECTS RESEARCH – Any research or clinical investigation that involves human subjects about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information about whom includes a subject's opinion on a given topic.

ICE NUCLEATION (also termed "seeding") – The point at which ice crystals are first initiated in a cryopreserved sample; usually applied in the context of controlled rate cooling.

IDENTIFIER/IDENTIFYING/IDENTIFIABLE INFORMATION – Information (e.g., name, social security number, medical record or pathology accession number, etc.) that would enable the identification of the subject. For some specimens this information might include the taxon name and collection number.

INCIDENT – Any unplanned occurrence that deviates from Standard Operating Procedures (SOPs) or applicable government laws and regulations during specimen retrieval, processing, labeling, storage, or distribution that may affect subsequent use of those specimens.

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, inducement, or intimidation.

INSTITUTIONAL REVIEW BOARD (IRB) – Any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of the research and conduct periodic review of such research.

LABEL – Any written, printed, or graphic material on or affixed to a specimen container or package.

LIFECYCLE (i.e., Repository Lifecycle) – A series of stages through which a repository passes during its lifetime.

LIQUID NITROGEN (LN_2) – Coolant used to cool and store samples. Nitrogen becomes liquid at -196◦C. Samples stored in the vapor phase of liquid nitrogen are -190◦C and warmer, depending on the distance from the liquid phase.

LIQUID NITROGEN DRY SHIPPER – A container used for sending samples in the vapor phase of liquid nitrogen.

LOT – A quantity of reagents, supplies or containers that is processed or manufactured at one time and identified by a unique identification number (see BATCH).

LYOPHILIZED – Dehydrated for storage by conversion of the water content of a frozen specimen to a gaseous state under vacuum. Also called freeze-dried.

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.

MORPHOGENETIC COMPETENCE (OR POTENTIAL) – Terms used to describe the state of cells that are able to respond to stimuli and in vitro manipulations and undergo morphogenesis, usually to produce differentiated structures comprising, shoots, roots and embryos.

NATURAL HISTORY COLLECTIONS (e.g., museums, herbaria, zoological and botanical gardens, aquaria, etc.) – Repositories that enable and perform object- or specimen-based scientific research, store a diversity of traditional specimens (e.g., live organisms, dried skins, skeletons, pinned insects, herbarium sheets, whole organisms in preservative, and microscopes slides) and often also frozen samples.

NECROPSY – See *AUTOPSY.*

OPERATING MANUAL (OPERATIONS MANUAL, MANUAL OF OPERATIONS) – Contains procedures, instructions, and guidance for use by operational personnel in the execution of their duties. Documents the step-by-step instructions on how to complete a task or handle a specific situation in the workplace.

PRESERVATION – Use of chemical agents, alterations in environmental conditions, or other means during processing and storage to prevent or retard biological or physical deterioration of a specimen.

PROCESS VALIDATION STUDIES – The process of demonstrating that a specific procedure will consistently produce expected results within predetermined specifications.

PROCESSING – Any procedure employed after specimen collection but prior to its distribution, including preparation, testing, and releasing the specimen to inventory and labeling.

PROSPECTIVE – A study or collection maintained for expected or likely use in the future.

QUALITY ASSURANCE (QA) – An integrated system of management activities involving planning, implementation, documentation, assessment, and improvement to ensure that a process or item is of the type and quality needed for the project. Same as Quality Management System (QMS).

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

QUALITY MANAGEMENT SYSTEM (QMS) – Same as Quality Assurance (QA).

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REPOSITORY – An entity that receives, stores, processes, and/or distributes specimens, as needed. It encompasses the physical location as well as the full range of activities associated with its operation. It may also be referred to as a *BIOREPOSITORY* or *BIOBANK*.

RETRIEVAL – The removal, acquisition, recovery, or harvesting of specimens (or data).

RETROSPECTIVE – Relating to or being a study or collection (as of a disease) that looks back on or deals with past events or situations.

SAFETY – Processes, procedures, and technologies to ensure freedom from danger or harm.

SAMPLE – A single unit containing material derived from one specimen.

SHIPPING MANIFEST – A written description of the contents of the shipped package.

SPECIMEN – In a clinical context, a specimen is specific tissue, blood, urine, or other material collected for analysis or a small fragment of tissue for microscopic study, taken from a single subject or donor at a specific time. In a biodiversity context, a specimen is (usually) an individual animal, plant, etc., or a part thereof used as an example of its species /population/etc., or type (known as type specimen) collected for scientific study, and/or stored as documentation of research.

STANDARD OPERATING PROCEDURE (SOP) – step-by-step instructions to be followed routinely for the performance of designated operations or in designated situations to achieve efficiency, quality output, and uniformity of performance.

STERILITY – Absence of detectable, viable, contaminating microorganisms.

SUBJECT – Also referred to as human subject. See DONOR.

TAXON – Any recognized category in the taxonomic hierarchy. For many purposes, the category "species" is the most important.

TELEMETRY SYSTEM – A system that allows for measurements to be taken from a distance, usually via radio wave transmission and reception of the information.

TG – The glass transition temperature marks the temperature at which a fluid becomes so viscous it appears solid. The extreme viscosity reduces diffusion and molecular restructuring, slowing reactions that might otherwise cause samples to deteriorate. The Tg for pure water is -132°C.

TOTIPOTENCY – In the context of plants, means that a single somatic (non-germ line) cell has the ability to differentiate along a developmental pathway and regenerate a plant. More generally, the potential for an undifferentiated cell to regenerate into a complete new plant.

VIRTUAL COLLECTIONS – Collections of virtual representations of specimens (e.g., digital pathology images, H&E stained slides, slides of tissue prepared for immunohistochemical analysis, digital images of specimens, molecular data) that are housed and analyzed elsewhere, or represent catalogs of specimens stored elsewhere.

VITRIFICATION (see also *GLASS TRANSITION*) - Refers to the transformation of a glass-forming liquid into a glass, which usually occurs upon rapid cooling. It is a dynamic phenomenon occurring between two distinct states of matter (liquid and glass), each with different physical properties.

WARM ISCHEMIA – The amount of time that an organ remains at body temperature after its blood supply has been stopped or reduced.

APPENDIX C: ABBREVIATIONS

Below is a list of abbreviations that are used throughout this document:

1D – One dimensional

2D – Two dimensional

cGCP – Current Good Clinical Practices

cGLP – Current Good Laboratory Practices

cGMP – Current Good Manufacturing Practices

cGP – Current Good Practices

CO_2 – Carbon dioxide

DNA – Deoxyribonucleic Acid

ESB – Environmental specimen bank

EDTA – Ethylenediaminetetraacetic Acid

H&E – Hematoxylin and eosin

IATA – International Air Transport Association

ICAO – International Civil Aviation Organization

ID – Identification Reference

IRB – Institutional Review Board

ISO – International Organization for Standardization

LN_2 – Liquid Nitrogen

MSDS – Material Safety Data Sheet

PBMC – Peripheral Blood Mononuclear Cell

PEL – Permissible Exposure Limit

PHI – Protected Health Information

QA – Quality Assurance

QC – Quality Control

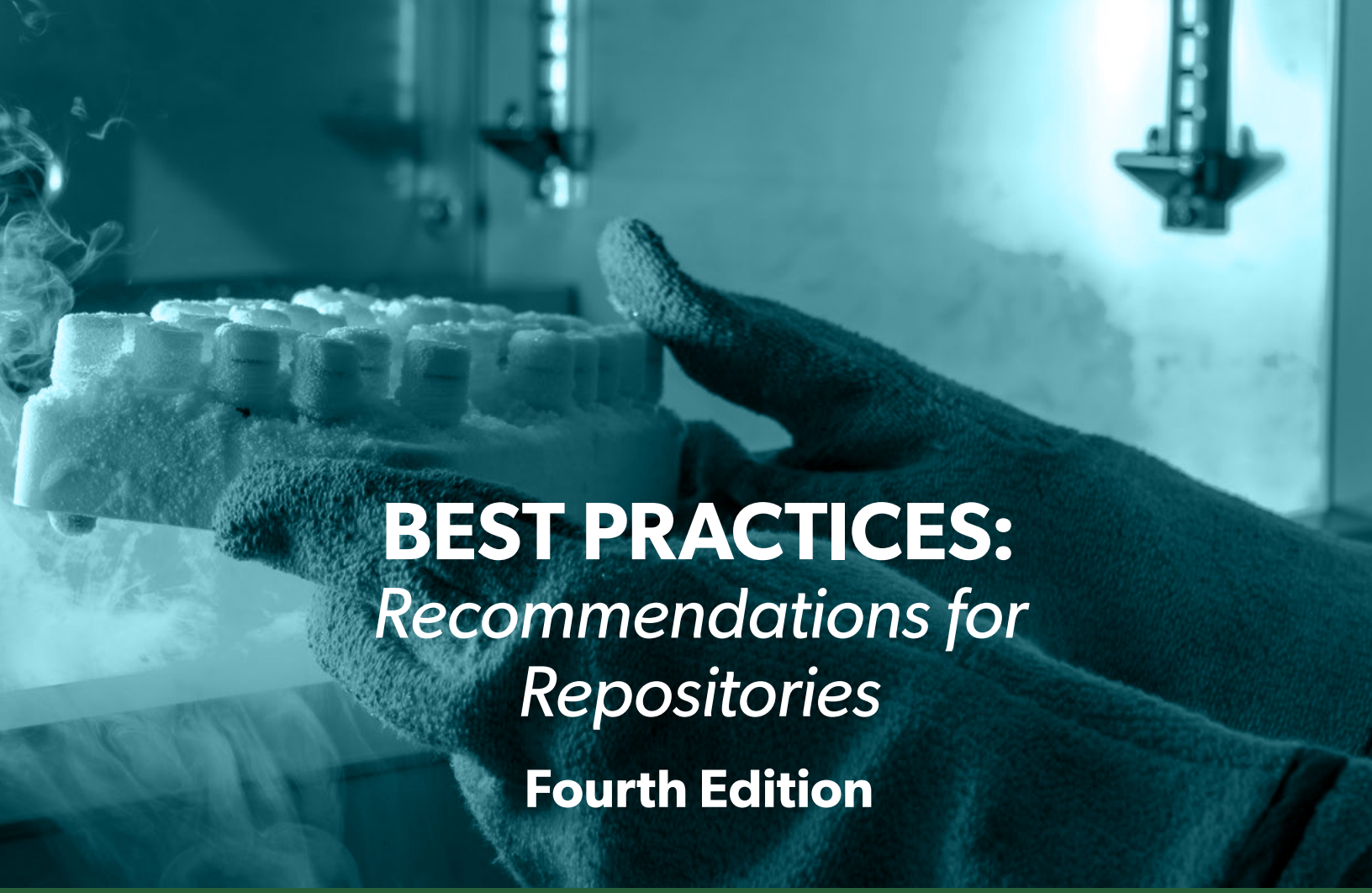
QMS – Quality Management System

RBC – Red Blood Cell

RNA – Ribonucleic Acid

SOP – Standard Operating Procedures

Tg – Glass Transition Temperature



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