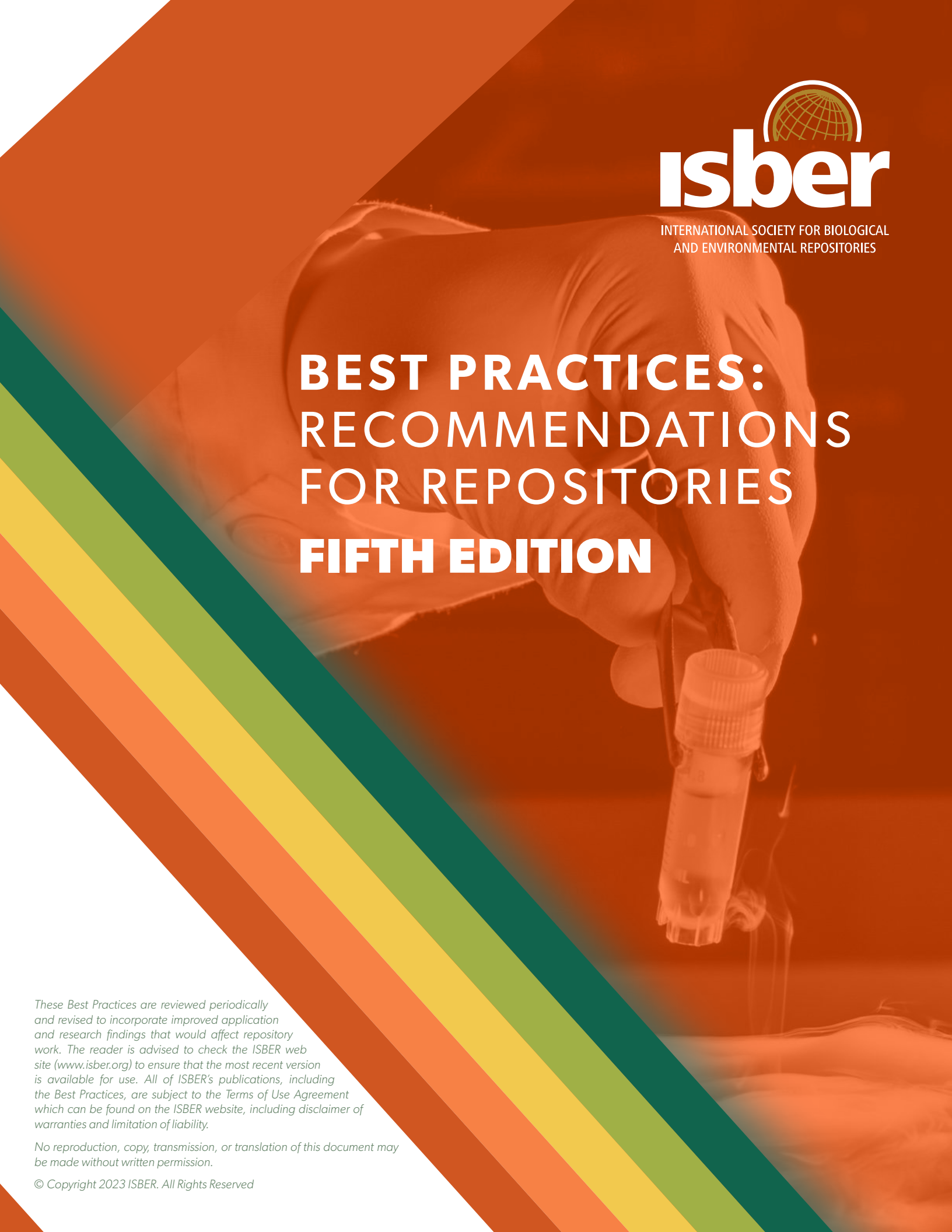

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INTERNATIONAL SOCIETY FOR BIOLOGICAL AND ENVIRONMENTAL REPOSITORIES

# BEST PRACTICES: RECOMMENDATIONS FOR REPOSITORIES

## FIFTH EDITION

*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. All of ISBER's publications, including the Best Practices, are subject to the Terms of Use Agreement which can be found on the ISBER website, including disclaimer of warranties and limitation of liability.*

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# Acknowledgements

The fifth edition of the *ISBER Best Practices: Recommendations for Repositories* reflects the substantial contributions of and reviews by repository professionals from diverse organizations worldwide in response to invaluable feedback provided by users of the previous editions. Representing the spectrum of human, biodiversity, environmental, and veterinary repositories, each of these dedicated individuals have shaped this edition through their expertise and commitment.

The editorial board extends our heartfelt appreciation to the ISBER Standards Community of Practice (CoP) and to the Gap Analysis Task Force who gathered and reported on user feedback, which was used as a primary input to the fifth edition. We also thank the fifth edition's Steering Committee, whose strategic insights have provided pivotal direction, enriching the content and purpose of this edition. We are indebted to the Chairs of the Standards CoP, Daniel Simeon Dubach and AnneMieke de Wilde, for their exceptional leadership and guidance. Their vision and dedication have been instrumental in shaping this edition. We are additionally grateful to Sheila O'Donoghue for her dedicated commitment to the communication plan to spread awareness of this edition.

We also extend our gratitude to Ana Torres, ISBER's former Executive Director (2015-2023) for her inimitable commitment and to the dedicated staff of Malachite Management for their administrative and organizational support, which have been essential in bringing this edition to fruition.

This edition, founded on esteemed prior editions of ISBER *Best Practices*, stands as a testament to the power of collaboration, encompassing the collective wisdom of contributors, user feedback, meticulous review, and visionary leadership. It is with pride that we present the fifth edition of the ISBER *Best Practices*, desiring that it will continue to serve as an invaluable resource for repositories worldwide.

# Contents

ISBER Head Office: 1618 Station Street, Vancouver, BC, V6A 1B6, Canada
Contact Information: T: +1.604.484.5693 • F: +1.604.874.4378 • E: *bestpractices@isber.org* • *www.isber.org*

ISBER Head Office: 1618 Station Street, Vancouver, BC, V6A 1B6, Canada
Contact Information: T: +1.604.484.5693 • F: +1.604.874.4378 • E: *bestpractices@isber.org* • *www.isber.org*

# ABOUT ISBER

The International Society for Biological and Environmental Repositories (ISBER) is the leading global forum that supports the development, management, and operations of repositories. ISBER fosters collaboration; creates education and training opportunities; provides a forum for the dissemination of state-of-the-art policies, processes, and research findings; and provides an international showcase for innovative technologies, products, and services.

One of these services provided by ISBER is the availability of a set of best practices specifically developed with biological and environmental repositories in mind. This fifth edition of the *ISBER Best Practices: Recommendations for Repositories* builds on the foundation established in previous editions published in 2005, 2008, 2012, and 2018 and is part of an ecosystem of ISBER-created or -endorsed tools. For more information about ISBER, see *www.isber.org*.

## INTRODUCTION

*ISBER Best Practices: Recommendations for Repositories* is a guidance document that reflects the collective experience of its members and other repository professionals.

This document provides clear guidance to novices and experienced professionals on how to recognize and fulfill their responsibilities, while offering practical advice on how to manage and support all types of repositories. In the context of this document, a repository is where part(s) of or entire organisms and/or environmental specimens and/or associated data are stored for safekeeping and distribution. Although the focus is on research and development, the fundamental principles and guidance offered herein for specimens and data management may also apply for other sectors and disciplines.

The term repository is used to refer to any entity focused on management of processes and activities around specimens and associated data intended *primarily* for research purposes. Alternative terms may include biobank, biorepository, biological resource center, collection (*e.g.*, microbial collection center, data collection center), cryogenic biobank, digital repository, biodiversity biobank seed bank, virtual biobank, veterinary biobank, culture collection, gene bank, environmental specimen bank, tissue bank, and cell bank among many others.

The *ISBER Best Practices: Recommendations for Repositories* (*ISBER Best Practices*) is designed for use by all types of repositories and biobanks around the world.

This document is intended to be of use to repositories operating within or for research sectors worldwide, as well as individuals or organizations that may be managing specimens outside the formal structure of a repository. The fundamental principles and guidance offered herein can additionally be applicable for other sectors and disciplines (including for analysis, development, and education). The *ISBER Best Practices* can form a foundation for repositories, guiding a repository's policies, practices, procedures, and operations.

## ABOUT THE FIFTH EDITION

The *ISBER Best Practices* are periodically reviewed and revised to reflect advances in research, technology, stakeholder expectations, and biobanking. This fifth edition of the *ISBER Best Practices* has been significantly revised in content and structure, based on ideas emanating from users' feedback on the previous edition. Additionally, the Cryo addendum previously published for the fourth edition has now been incorporated throughout the document. This collated feedback provided valuable insights detailed in a resultant gap analysis report that was used to direct the scope of work for the development of the revised document.

## THE *ISBER BEST PRACTICES* COHERENCE WITH OTHER EXISTING SOURCES

The *ISBER Best Practices* are part of a landscape that includes regulations, standards, and guidelines among other resources. Differences exist between regulations, standards, and best practices or guidelines and each fulfills a specific function.

- Regulations are legal mandates and may apply at different levels (*e.g.*, local, federal, national, regional, or international). Understanding related obligations starts with building awareness of what regulations and legislation apply, and is aided by a culture of compliance.
- Standards are largely voluntary and use may be driven by the particular industry, stakeholder expectations, or end-user needs. Implementation of and assessment to a standard helps to demonstrate the repository's commitment to uphold the requirements stipulated in that standard.

- Guidelines, such as the *ISBER Best Practices*, are discretionary and represent a consensus of the community experience and expertise. They offer general information, explanations, examples, advice, and recommendations that can be selectively adopted as applicable to the repository context.
- Organization Obligations: In addition to external factors, organizations may also have separate obligations relevant to their organization and/or stakeholders.

The *ISBER Best Practices*, fifth edition document reflects feedback on the previous fourth edition generously provided by the user community, as well as expert consensus of ISBER members and others. Where known or identified, existing relevant external standards, norms, and guidelines were considered, along with a repository's need to observe organizational obligations. This supports coherence with obligations and advice from other sources.

## HOW TO NAVIGATE THE DOCUMENT

The *ISBER Best Practices* comprises 12 interdependent sections that each focus on a particular topic. These sections have been ordered to broadly follow the logic for establishing a repository, covering aspects of a repository's lifespan from initiation through closure. Section headings may be used to quickly navigate from the Table of Contents to a topic of interest. This edition of the *ISBER Best Practices* includes extensive cross-references to other section locations containing related content. This both improves navigation through the document for a particular topic while also limiting duplication of content in different sections. Because of this, sections can be read independently and the cross-references will guide you to other sections that may be of additional interest or constitute essential reading for a particular context.

Additionally, the *ISBER Best Practices* includes Appendices to facilitate the use of the document and help find additional external information on specific topics. These are:

- **Appendix A: References and Internet Resources.** These resources are referenced within the relevant section(s), and additionally compiled in one place within Appendix A.
- **Appendix B: Terminology.** See below for more information about the Terminology section.
- **Appendix C: Abbreviations.**

## WHAT ARE THE PRACTICES AND HOW TO FIND THEM IN THE DOCUMENT

Within the *ISBER Best Practices*, there are different types of practices. Throughout this document, practices are presented in-text, and can be identified by the use of the words "can", "may" or "should" in the context of an action or activity the repository can undertake. The term "Best Practice" is used where a level of operation is indicated that is above the basic recommended practice or more specifically designates the most advisable practice.

During the fifth Edition revision process, both newly proposed and existing best practices were assessed for content and inclusion using the OECD DAC Network on Development Evaluation (EvalNet) tool. This tool presents six evaluation criteria against which new practices are judged: relevance, coherence, effectiveness, efficiency, impact, and sustainability. These criteria and guidelines for use are available on the OECD EvalNet tool; see *https://www.oecd.org/dac/evaluation/daccriteriaforevaluatingdevelopmentassistance.htm*.

## HOW TO APPLY THE PRACTICES

Adherence to the guidance provided by the *ISBER Best Practices* is voluntary. The *ISBER Best Practices* includes a wide variety of practices that may or may not apply to a particular repository. Based on the repository's characteristics (*e.g.*, purpose, size, type of organization, or regulatory environment), practices can be evaluated for repository relevance and application. A repository can then apply relevant practices to their operations, including implementing strategies such as planning, risk, and quality management, and information and inventory management software solutions to implement the practices. Where organizational policies are lacking or a repository wishes to implement a new standard, the practices can be used to help inform suitable strategies.

It is understood that physical location or financial or other constraints can make "Best Practices" difficult or not feasible to attain. Readers are advised to ensure that recommendations are appropriate for their particular repository type before application. Repositories facing such challenges can decide whether they are able to incorporate these recommendations and may instead incorporate them into plans for future improvements to the repository.


ISBER Head Office: 1618 Station Street, Vancouver, BC, V6A 1B6, Canada
Contact Information: T: +1.604.484.5693 • F: +1.604.874.4378 • E: *bestpractices@isber.org* • *www.isber.org*

## USE OF TERMINOLOGY THROUGHOUT THIS DOCUMENT

Over time, changes are made to existing terms, and new terms emerge that affect the accuracy and clarity of terminology within a document. Reflecting this and prompted by the user feedback, the terms and their use have been extensively reviewed as part of the development of the fifth edition of the *ISBER Best Practices*. Existing and new terms and definitions were evaluated and where necessary, updated to:

- Improve clarity.
- Align with other definitions.
- Relate better to the section topic.

Generally, the terms are defined in the context of this document and biobanking as a field. In some cases, the terms might be used differently in different fields or contexts, or alternative synonyms used. Cognizant of this, term definitions have been provided in plain language, avoiding technical jargon and repetition of the term itself to enhance understanding. This also facilitates translation to other languages. Additionally, the use of terms throughout the document was standardized and aligned to provide additional consistency and clarity.

In particular, ISBER recognizes that the definition and subsequent use of the terms "specimen" and "sample" varies when used in clinical versus biodiversity and/or environmental settings. While "specimen" is used predominantly throughout the document, it could be substituted for "specimens and/or samples" in most instances. In recognition of the fact that the data associated with specimens is generally critical for the end-user, the terms "specimens and/or associated data" and "specimens and/or data" have been extensively applied throughout the document.

# SECTION A: GOVERNANCE, PLANNING, MANAGEMENT, AND COMMUNICATIONS

## A1. GENERAL INTRODUCTION TO REPOSITORIES

Much of biological analysis and research depends on the ability to access significant aggregations of biological and environmental units (specimens) that are described in great detail (data). These collections are known by a multiplicity of terms across the world depending on field of use and applications, and are subsequently referred to as *repositories* for the purpose of this document. Repositories are established with a diversity of goals and objectives, sizes, and intended uses (see *A1.1. Types of Repositories*). Good management ensures that:

- The purpose and mission (meaning the objectives and approach to achieving them) of the repository are clearly defined (repository and business planning).
- Policies and procedures to manage the repository are established, documented, and are followed (governance).
- Plans for technical operation of the repository are addressed (operations planning and quality management).
- The repository is properly resourced and financially sustainable for the duration of the intended period of operation, to ensure it fulfills its mission (business planning).
- Personnel roles, responsibilities, and accountabilities are clear and day-to-day operations are effectively managed to optimize efficiency (repository operations).
- The repository communicates regularly to stakeholders (communications).

The depth and breadth of such management often differs from repository to repository. Regardless of the repository structure, appropriate planning, oversight, and communication to enable a repository to fulfill its mission should be addressed.

### A1.1. Types of Repositories

Repositories should have procedures addressing the life cycle for each type of specimen and associated data held. Accordingly, repositories are diverse and can differ in terms of a number of characteristics, including collection purpose, organism or material types stored, collection format, financial resources, organizational structure, and retention time.

**Collection purpose:**

Specimens and associated data may be collected as a part of prospective or retrospective studies and the methods of collection, processing, and distribution of these specimens (see *Section J. Specimen Collection, Processing, Receiving, and Retrieval*) may depend on resource or legal constraints, and the particular scientific inquiry under consideration.

Repositories are often organized according to the type of research they serve; examples include population cohort; epidemiologic, disease-oriented studies; clinical trials; or pathology archives. Biodiversity repositories and environmental specimen banks (ESBs) are often associated with natural history collections, universities, veterinary, environmental, or agricultural organizations.

Specimens and data may have been collected by individuals specifically to address their own research purposes, through surveys, or as part of generic collecting expeditions. Such collections often provide a source of material to the wider scientific community, to help safeguard biodiversity and document environmental change.

The collection purpose of a repository should be clearly outlined during the repository initiation and planning phase (see *A3.1. Repository Planning*).

**Specimens and data stored:**

The collection and storage of specimens and associated data from various organisms (*e.g.*, human, animal, plant, fungal, bacterial, and environmental) can be performed in support of a variety of research endeavors.

**Collection format:**

Repositories can store specimens and data collected by a single researcher, laboratory, or organization for a defined research purpose. Alternatively, repositories can have multiple depositors and end-users for a large number of studies as part of a centralized repository service and act as the custodian of the collection(s).



ISBER Head Office: 1618 Station Street, Vancouver, BC, V6A 1B6, Canada
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Decisions about which specimens and/or data are collected can be made by individual researchers, a team of researchers, or the repository custodian or director. These decisions are informed by factors including repository purpose; study goals, where relevant; and stakeholder(s) needs (see *A3.1. Repository Planning*).

Specimens and associated data can be collected and stored on-site, at a contracted or associated storage facility, or virtually (see *Section I3.5. Virtual Platforms*). In some cases, repositories may focus solely on data that describes the specimens and the results of analyses (*e.g.*, genetic data, phenotypic data, etc.).

**Financial resources:**

Repositories may be funded in a variety of ways, *i.e.*, from public, private, or blended sources:

- Public or philanthropically-funded repositories may exist within museums, research centers, laboratories (based at universities or in government institutions), or hospitals.
- Academic biobanks are research-driven and are often supported by host institutions and public funding in the form of grants.
- Governments sometimes create repositories to support the public good, such as seed banks for public food safety in case of a disaster.
- Commercial or private biobanks are often more business-oriented with strategies for dedicated paid-for services and/or the development of products.

Despite these differences, outlining how a repository can maintain its financial sustainability is key to survivability (see *A3.2.2.3. Financial Sustainability*). Furthermore, a repository can explore options for public private partnerships that align with the stakeholder needs (see *Section D2. QM Roles and Responsibilities*).

**Organizational Structure:**

Some repositories operate as independent legal entities or as part of a parent legal entity. Additionally, several organizations or repositories participate in multi-repository consortia or networks, either on a temporary or permanent basis. Repositories may be operated by repository personnel or through contracted repository services.

**Retention time:**

Retention time impacts overall repository capacity, long-term accessibility, quality management, as well as operational and capital expenses. It can span vastly differing lengths of time, depending on many factors, including the purpose of the repository. For an in-demand collection and where accessibility is promoted, retention time might span days, weeks, or months; or it might be measured in years or decades; or it might be indefinite, as for some precious or rare specimens. Legal and ethical considerations often influence retention time. Calculation of retention times may also account for access rates, provenance information, data associated with the specimens, quality, and overall usefulness of specimens and data (see *Section J1. General Introduction to Specimen Collection, Processing, Receiving, and Retrieval*). Additionally, the retention time is an important factor in determining the repository facility design (see *Section G. Facilities*).

Regardless of the characteristics of repositories, a caretaking responsibility for the specimens and associated data in their collections exists. This is often referred to as custodianship. The obligation extends throughout the specimen and associated data life cycle including collection, storage, distribution, research, repository closure, and specimen and data destruction. Custodianship includes overseeing the quality and integrity of the specimens and associated data, protecting the rights and welfare of donors/participants (including the privacy of participants and the confidentiality of their data), and ensuring that the uses of specimens and associated data are appropriately governed.

Repositories should identify the custodian (who may be the repository director) for their collections and develop a custodianship plan (which may be a section of a business plan if one is being developed). In the absence of a business plan, a separate custodianship plan must be developed. This plan should address the options for continued custodianship or other when there is a loss of funding, when the objectives of the repository have been accomplished, and/or the repository closes. It also addresses a plan, in agreement with appropriate stakeholders, for what happens to the collection if the custodian leaves.

The characteristics of an individual repository influence the governance structure, business plan including financial support, and operational planning and execution required. Just as specimens and associated data should be fit-for-purpose for the repository's end-users (see *Section D1. General Introduction to Quality Management*), the planning and execution of the repository should be fit-for-purpose as well.

***BEST PRACTICE:*** The repository should identify the key characteristics of their repository at the outset and develop their repository operations, business plan, and governance to align with the repository needs.

## A1.2. Lifespan and Phases of a Repository

The *lifespan* of a repository describes the activities of a repository from its conception to closure. This differs from the *life cycle* of a specimen (see *Section J1. General Introduction to Specimen Collection, Processing, Receiving, and Retrieval*).

Regardless of the type of repository, there are several distinct phases that define the lifespan of a repository. A *phase* is a period of time within a repository's lifespan that may have distinct activities and implications for business, governance, and/or operational planning. The type of repository may impact the duration and activities that may occur in each phase of its lifespan, but it is good practice for repositories to identify their current phase and plan activities, governance, business, and operations according to that and potential future phases.

Repository phases generally align with five stages[1,2] (see Figure A1. Phases of a Repository):

- **Initiation:**

During initiation phase, the goal/purpose of the repository should be well-thought out and defined with a business case identified for creation of the repository. During this phase, a basic business plan may be developed along with a governance model that aligns with the repository's legal framework.

- **Planning:**

During the planning phase, the scope of activities of the proposed repository should be defined (see *A3.1. Repository Planning*). It is during this phase that initial governance should be established, including plans for specimens and data collection and management, review of organizational policies, and regulatory compliance requirements. Financial factors should be addressed during this phase (see *A3.2.2. Financial Considerations*), and operational plans drafted (see *A4.4. Operations Plans*).

Planning should also include:

- The data to be collected, managed (see *Section I2. Data Management*), and shared (see *Section K2. Access, Distribution, and Use*)
- Personnel required (see *A4.2. Repository Personnel*)
- Space and facility design (see *Section G. Facilities*)
- Equipment needed (see *Section H. Storage and Processing Equipment*)

Risks should be assessed to contribute to a risk management plan (see *Section B1. Risk Management*). Key stakeholders should be enlisted in this phase to partake in the business planning process for the sustainability of the repository, which should include plans for a potential termination or closure.

- **Execution:**

The execution phase of a repository is when the activities identified in the planning phase are put into place. This may include hiring personnel; purchasing equipment; qualifying or validating equipment and processes; establishing quality management, including policies and standard operating procedures (SOPs) (see *Section D3. Quality Planning*); and managing ethics and regulatory compliance (see *Section C. Ethical, Legal, and Social Implications*).

As new services or activities are added to an already established repository or if the type of repository changes (*e.g.*, individual repositories are combined into an institutional repository), the planning and execution phases may be re-visited and repeated as needed.

- **Monitoring:**

The monitoring phase could also be referred to as the operational or maintenance phase. This is when the repository has been established and activities, including specimen and associated data collection, are underway. During this phase, progress may be monitored against the plans created in the execution phase *e.g.*, quality assessment (see *Section D3.5. Quality Control Approaches*), or performance based on key performance indicators (see *Section D3.8.4. Key Performance Indicators*). Risks should be monitored and mitigated with the goal of preventing chances of disruption of repository activities. Accreditation or certification may be obtained in the execution or monitoring phase depending on the type of repository and services provided (*e.g.*, in the US, CLIA certification is needed if specimen data are used to inform patient care). The activities in this phase may change as the services and activities of the repository itself shift to accommodate the needs of the repository and its stakeholders.

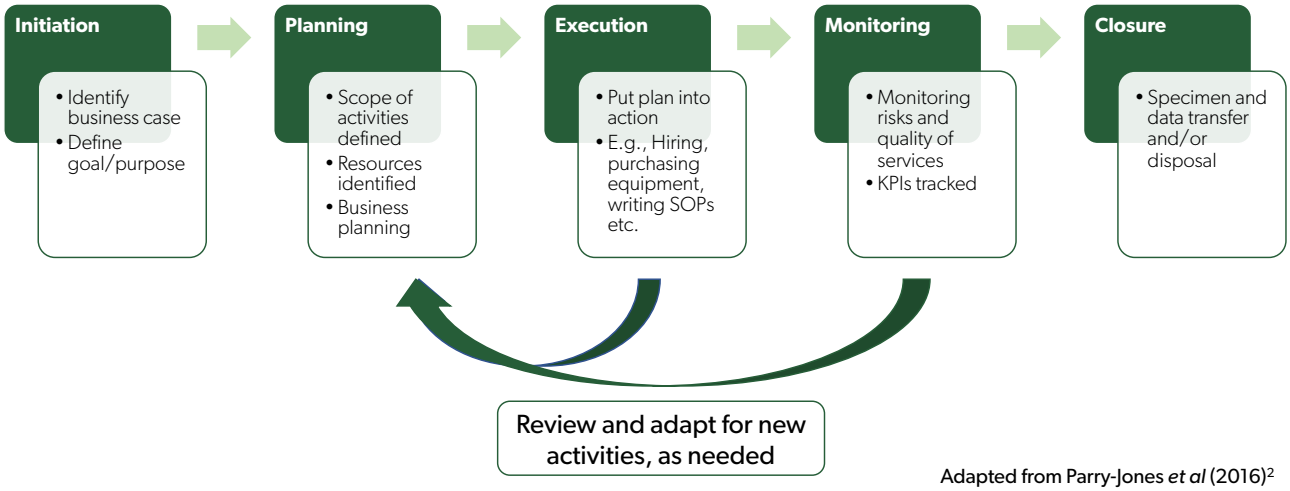
- **Closure:**

The closure phase of a repository may or may not be relevant to all repositories but nevertheless should be taken into account from point of repository initiation and revisited on an ongoing basis (see *Section K4.4. Legacy Planning*). Closure is



ISBER Head Office: 1618 Station Street, Vancouver, BC, V6A 1B6, Canada
Contact Information: T: +1.604.484.5693 • F: +1.604.874.4378 • E: *bestpractices@isber.org* • *www.isber.org*

likely to impact some of the collections within a repository (*e.g.*, a project-associated collection) or the entire repository. It may be triggered by a planned end of a collection, or an unanticipated end due to a natural disaster or sudden withdrawal of funding resources. Closure of a repository may also be the result of a political or strategic decision. In all cases, the closure or transfer of a repository should be planned for in the business and operational plans (see *Section K4.6. Transfer to New Custodian*). The goal in repository closure should be to appropriately transfer or dispose of specimens and associated data in a way that aligns with regulatory requirements and the ethical framework (see *Section C. Ethical, Legal, and Social Implications*).




Adapted from Parry-Jones *et al* (2016)[2]

**Figure A1:** Phases of a Repository

***BEST PRACTICE:*** Repositories should identify and periodically review what phase of their lifespan they are in and plan their activities, governance, business plans, and operations according to that phase and potential future phases.

## A2. GOVERNANCE

Governance plays an important role in the success of and level of confidence in organizations within a society. Different international sources provide valuable information for effective governance principles and strategies[3,4].

### A2.1. Repository Governance

Repository governance is the design, implementation, and oversight of policies and procedures that regulate operations. Governance encompasses the system by which a repository is controlled and operates, and the mechanisms by which it, and its people, are held accountable. Ethics, risk management, compliance, and administration are all elements of governance. Governance structure, design, and complexity may vary greatly by repository size, purpose, source of support, and institutional or organization affiliation. Governance structure should comply with applicable local, national, and federal regulations; provide good stewardship of repository specimens and data; and include quality control through quality management adherence (see *Section D. Quality Management*). Governance oversight may be provided by an individual, committee, board, or other group (*e.g.*, governance oversight body) that serves to guide and advise the repository. In the case of smaller repositories, governance may be the responsibility of a few people rather than a large oversight committee. A governance framework and/or policy should be developed to include a description, composition, and responsibilities of the individuals or bodies that have governance oversight. Depending on the type and structure of the repository, the body may be a legal entity that has legal rights and responsibilities for all its activities[5].

Clear terms of reference in relation to the scope and limitations on the governing body should be set up by the repository to avoid conflicts of interests and promote clear management structures.

***BEST PRACTICE:*** Terms of reference (TOR) should be developed to define the purpose, structure, and composition of the governing body and should be openly available.

***BEST PRACTICE:*** Repository leadership should review governance policies and procedures periodically and final versions should be made available to stakeholders, as appropriate.

## A2.2. Governance Structure

The type of repository, its size, the services it provides, location, and other factors can all influence the governance structure. The size and functions of any governance structure may also depend on whether the repository is a stand-alone facility or part of a larger entity. A repository governing body or committee is an authorized group of people who provide oversight, guide strategic decisions, form policy and steer the overall direction of the repository. Regardless of the size of the governing body, all the functions and expertise required to properly govern the repository should be identified and be involved in repository governance.

There is more than one model for an effective governing body. Some may have operational control, whereas others are limited to an advisory role that provides oversight but not direct managerial control. It may also be formed to provide a high-level leadership function, *i.e.*, setting strategy, which is then implemented by repository management. Individuals on the governing body will generally be selected for their expertise and/or represent key stakeholders.

Where the repository is multi-organizational (*e.g.*, a consortium of different organizations), the governance structure should reflect this, with supporting multi-party contracts or legal agreements in place to further underpin roles, responsibilities, accountability, and transparency.

The repository governing body should include or have access to expertise that covers the following functions:

- Finance and business management.
- Regulatory and/or quality management.
- Legal.
- Ethics including bioethics.
- Scientific expertise (relevant to the repository's holdings).
- Health and safety.
- Data and computer systems.

Where the repository forms part of a larger department or organization, these functions may be carried out by individuals or bodies outside the main management structure of the repository. Nevertheless, the repository, or its wider institution, should be able to demonstrate how it ensures that these functions are carried out.

Consideration for membership to a governing body should be given for representation (where appropriate) from:

- Host institutions.
- Funding bodies.
- Donors (source of specimens and/or associated data).
- End-users.
- Lay public.

The governing body should ensure that a strategic plan for the repository is established with appropriate management accountability and audit to ensure that the plan is carried out. The repository leadership should report periodically to the governing body on all aspects of repository management and operations.

Importantly, the governing body as a collective unit, rather than any single individual, should make strategic decisions and monitor their implementation on behalf of the repository and its stakeholders. Effective governance means having rules, structures, and processes that are capable of achieving the objectives set out for the repository.

## A2.3. Governing Roles and Responsibilities

The primary job of the governing body is to protect the rights, interests, and wellbeing of all the stakeholders on behalf of the repository. Good governance requires the governing body to act objectively, ethically, honestly, and with the utmost integrity. The governing body as a whole does this by making sure the repository runs smoothly and can achieve the goals and objectives it has promised to deliver to its stakeholders, in accordance with relevant regulatory and legal obligations. Governance is generally concerned with the big picture aspect of these roles and responsibilities, rather than the day-to-day management of the repository. It works more effectively when the governing body, management, and personnel have a clear commitment to and shared understanding of these roles and responsibilities, and how they work within the repository (Tables A1 and A2).



ISBER Head Office: 1618 Station Street, Vancouver, BC, V6A 1B6, Canada
Contact Information: T: +1.604.484.5693 • F: +1.604.874.4378 • E: *bestpractices@isber.org* • *www.isber.org*

**Table A1:** The Roles the Governance, Management, and the Personnel Hold within a Repository

| Organizational Structure | Role |
|---|---|
| Governing Body | Represent the stakeholders; plan strategic direction, set the repository's goals; oversee the repository, its financial direction, policies, and accountability; supervise and evaluate management; approve fee structure. |
| Management | Implement strategic plans, goals, and policies made by governing body; administration; financial management (including proposing a fee structure); develop personnel policies; and organize, supervise, evaluate, lead, and inspire personnel. |
| Repository Personnel | Perform duties under the instructions and direction of management, support governing body in their roles. |

**Table A2:** The Responsibilities Associated with Governance Roles

| Governing Role | Governing Responsibility |
|---|---|
| Lead | Represent all stakeholders ensuring they can participate and be heard; create vision; advocate, negotiate, and maximize self-determination. |
| Plan | Set overall direction, purpose, future strategies, goals, ethics, and values for the repository. |
| Organize | Develop policies and governance arrangements; interact with management; guide relationships, alliances, and collaborations with the public and among stakeholders. |
| Control | Ensure the repository is accountable, legal, and financially stable; hire, support, and oversee the performance of the senior management; monitor overall outcomes. |

***BEST PRACTICE:*** Prior to starting repository operations, a repository should have an appropriate governance structure with established and transparent policies and practices that cover the full repository lifespan and are appropriate for the type and phase of the repository.

***BEST PRACTICE:*** The repository should specify the governing body members' responsibilities, accountabilities, authorities, and interrelationships.

### A2.4. Policy Development

Policies provide a high-level roadmap including boundaries for operations (see *Section D3.1. Quality Manual*), whereas procedures, including SOPs, provide the granular details pertaining to the processes for carrying out day-to-day operations (see *Section D3.3. Standard Operating Procedures*). Policies work to ensure achieving long-term goals, but do not detail exact steps for performing particular actions helping to reach these objectives. Instead of focusing on step-by-step instructions, they give direction for the development of standard operating procedure(s) and reinforce them. Policies exist to ensure that personnel will perform in a consistent way that best serves the goals and objectives of the repository, in a given situation[6]. They should provide guidance, consistency, accountability, and efficiency, as well as ensuring compliance with existing regulatory frameworks and approvals, regulations, and applicable laws. Additionally, policies can help streamline internal processes and can be used as a resource when training repository personnel (see *A4.2. Repository Personnel* and *E2.2. Competence Assessment*). Policies connect the repository's mission to its procedures.

Policy development is the process of deciding what should be achieved, what should be done to achieve it, how it will be achieved, and who should do it. The policy development process should be undertaken during the repository's planning period. This helps determine the repository's operational direction. It also is important to develop policies that allow enough flexibility for future changes.

Policy development includes the following steps that are undertaken by repository governance and management:

- Identifying the topic and the context to be addressed by the proposed policy.
- Discussing the need and content of the proposed policy.
- Writing the policy.

- Approving the policy.
- Implementing the policy.
- Regularly reviewing and evaluating the policy.

A repository can consider the following guidance when developing policies:

- Keep it simple. Policies should be written in plain language.
- Keep it general. Policies cannot address all possible situations.
- Make it relevant to the context.
- Check for accuracy and compliance.
- Ensure the policy can be enforced.

Policies should be reviewed at predetermined, regular intervals or as needed based on the changing processes and/or needs of the repository.

***BEST PRACTICE:*** Policies should be developed with the full repository lifespan in mind.

### A2.5. Elements of a Repository Governance Plan

It is important to keep in mind that the governing body should not take full responsibility for executing the governance plan. Rather, while governing bodies are positioned to form the governance plan, they should effectively delegate duties to appropriate parties to carry out its execution. In general, when establishing or enhancing a governance plan the following should be considered:

- The applicable regulatory, governance, or legal requirements for the repository.
- Provisions for safekeeping of the collection including custodianship, maintenance, security, and integrity of specimens and data (see *Sections G. Facilities*; *I. Information Management*; and *J. Specimen Collection, Processing, Receiving, and Retrieval*).
- The key accountabilities for the relevant levels of authority.
- The relationship and interactions between the governance requirements, operational functions, and business requirements.

Basic components of a good governance plan should include the following:

- **Structure** - organizational design, objectives, reporting structure, management roles, and responsibilities.
- **Oversight Responsibilities** - oversight and responsibilities, management accountability and authority, decision-making process.
- **Talent and Culture** - strategic leadership; business and operating principles; development of personnel.
- **Infrastructure** - policies and procedures, reporting and communication (see *A5. Communication and Repository Promotion*), technology.
- **Transparency** - regarding governance structure, membership of any governing body, and policies regarding specimen and data access and use including applicable requirements, limits, exclusions, and priorities (see *Section K. Access, Distribution, Use, Transfer, and Disposal*; and *Section I. Information Management*).

***BEST PRACTICE:*** A widely distributed, readily available, written governance plan should be created and regularly reviewed.

## A3. REPOSITORY AND BUSINESS PLANNING

### A3.1. Repository Planning

Repository set-up begins with the initiation phase and continues through both the planning and execution phases of the project (see *A1.2. Lifespan and Phases of a Repository*)[7]. During the initiation phase, the research focus for the repository should be explored and defined in depth. Through market research, discussions with stakeholders (see *A5.2. Communication Strategy and Plan*), and other methods, the niche, purpose, and the need for the repository should be evaluated to ensure unique added value for potential contributors and users of the repository. This process should include:

- Justifying the need for a new repository, *e.g.*, by evaluating existing repositories supporting the same field of research or scientific endeavor.
- Identifying potential for participants/donors or providers, *e.g.*, representing a unique group or enabling research to address a previously unmet need.



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- Engaging likely end-user(s) and identifying their requirements (in terms of aligning scope and scale of specimens and data to the need).
- Evaluating the potential impact (including environmental).
- Identifying opportunities for funding or financial support to evaluate the sustainability of the repository (see *A3.2.2. Financial Considerations*).

Once it has been determined that the repository fulfills a need within the research community, the mission (*i.e.*, its objectives and how it will fulfill those objectives) of the repository should be clearly defined. The repository should identify end-user requirements including the planned use of specimens and data (see *A3.1.1. Specimen Collection and Storage Environment*) and the services to be provided (see *A3.1.2. Services to be Provided*).

During the planning phase, it is important to establish the governance (see *A2.1. Repository Governance*) and financial structures (see *A3.2.2. Financial Considerations*) that will support the repository's mission. Plans for the collection, processing, storage, and distribution of specimens and associated specimen data should be established early during this phase as these will impact both the infrastructure and facilities required (see *Section G. Facilities*) as well as the expectations of donors/participants and end-users. The repository should consider the need to align with stakeholder expectations when developing these plans. There are many considerations to be made when planning a facility with the ultimate goal to support the needs of the repository and end-users and considering any relevant local, national, or international standards and statutory guidelines. Operational management structures (see *A4.2. Repository Personnel*) and personnel levels should be established during this phase and take into account any ancillary laboratory services that will be contracted out (see *A4.3. Contracting Services and Consultants*). Prior to moving into the execution phase, the repository should review the plans against the previously defined mission to ensure fitness for purpose of the plans and arrangements.

The mission should be reviewed regularly during the monitoring phase (see *A4. Repository Operations*) and throughout the lifespan of the repository to ensure it remains relevant to the changing needs of its end-users. This may require further cycles through the earlier phases of repository set-up.

***BEST PRACTICE:*** The plan to initiate a new repository should include evaluation of all relevant factors that justify and inform the need for a new specimen and/or data collection and include a strategy to establish a repository capable of success in its mission.

### A3.1.1. Specimen Collection and Storage Environment

The repository should endeavor to ensure that the specimens and associated data are fit for purpose (see *Section D1. General Introduction to Quality Management*). This will depend on the goals of the research effort supported and the intended use. Specimen type, quantity, specimen source, downstream testing plans, and financial constraints may influence decisions regarding specimen collection (see *Section J4. Collection Considerations*).

In advance of introducing new types of specimens and/or data, the repository should plan how the specimens and associated data will be collected, managed, and accessed and ideally have this documented (see *Section J8. Specimen Inventory Management*). The specimen collection plan should include the scale of collection and optimal numbers; exclusion criteria, if any, for specimens that prove difficult to collect; and defined acceptance criteria where legacy specimens are acquired. Collections plans should be revisited and revised, as needed, (e.g., when changes are made to the potential end use of the specimens) to ensure continued fitness for purpose. The repository should determine the most appropriate storage environment(s) for the types of specimens it holds (or plans to hold in the future) considering intended use(s) and ensure that the necessary facilities (see *Section G. Facilities*), equipment (see *Section H. Storage and Processing Equipment*), and funding are in place to support the storage of these specimens until they are needed for use.

Policies should be established for the acquisition of new specimens, use of specimens, and for disposing 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 or data or both (see *Section K4. Transfer and Disposal*).

A repository may be established to centralize collections (either physically or virtually) or to store legacy collections. Acquisition of previously collected or legacy specimens and associated data should be made on the basis of predefined acceptance criteria, both technical and contractual.

***BEST PRACTICE:*** The research purpose of the specimens and data should be defined prior to collection to ensure the methods for collection, processing, and storage are fit for purpose.

### A3.1.2. Services to Be Provided

Repositories should determine the services to be provided based on the type of repository, access to resources, and the services required by stakeholders. Services may include:

- Specimen and data collection/acquisition.
- Receipt / accessioning.
- Specimen processing, *e.g.*, specimen preparation and aliquoting, histology, micro-dissection, nucleic acids extraction, viability assays, etc.
- Specimen cryopreservation.
- Quality control of stored or collected specimens and associated data.
- Specimen testing (*e.g.*, immunohistochemistry, DNA sequencing, etc.).
- Specimen tracking.
- Data management.
- Data analysis.
- Specimen storage.
- Specimen and data distribution.
- Technical support for end-users of specimens and data.
- Provision of quality control specimens for testing.

Other services may not be directly associated with specimen and data handling. These may include:

- Feasibility assessment to assist with study planning and proposal submissions.
- Biobanking advice, *e.g.*, selection of specimen containers, labeling schemes, storage and distribution recommendations.
- Providing letters of support or the establishment of collaborative relationships.
- Supporting regulatory submissions.
- Identifying and/or consenting of donors/participants.
- Services related to the facility or infrastructure, including introduction and maintenance of storage units, *e.g.*, freezers and other equipment.
- Providing educational courses.

All services offered should be well-defined and appropriate infrastructure should be put into place to ensure that specimens, associated data, and/or services are considered fit for purpose (FFP) for research purposes according to defined criteria (for more information on fit for purpose, see *Section D1. General Introduction to Quality Management*). The infrastructure should include equipment and supplies as well as the trained and competent personnel to perform these services. The repository should consider cost recovery and the provision of services to offset the costs of providing these services, where appropriate (see *A3.2.2.2. Cost Recovery*).

***BEST PRACTICE:*** Repositories should clearly define what services are provided and the fees for providing those services.

## A3.2. Business Planning and Sustainability

A business plan may also be referred to as a management plan, and is of particular use to the development of a repository, even for small repositories and those operating in the public domain. The primary purpose of a business plan is to plan for the repository's future, including its technical and financial feasibility. These plans should include goals or milestones alongside detailed steps of how the repository will reach each milestone. The process of creating a roadmap for achieving the repository's goals will help determine the business focus and sustainability.

Business planning should include identifying:

- Potential end-users (see *A5.2. Communication Strategy and Plan*).
- Stakeholder needs and infrastructure (*e.g.*, see *Section G. Facilities*).
- Resources, *e.g.*, personnel (see *A4.2. Repository Personnel*) and equipment (see *Section H. Storage and Processing Equipment*).
- Services (see *A3.1.2. Services to be Provided*) to meet those needs (see *A3.1. Repository Planning*).

See *A3.2.3*. for more details regarding the components of a business plan. The plan should be reviewed at routine intervals or as necessary to account for changes in organizational structure, funding, labor, materials, supplies, etc.



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***BEST PRACTICE:*** A business plan should be developed for the lifespan of the repository and should be reviewed and updated on a regular basis or as requested.

### A3.2.1. Repository Sustainability

Long-term sustainability of the repository covers many different aspects, which can be classified in a framework of four partly overlapping components[8, 9].

- Operational (*e.g.*, processes, quality management): Repositories should make operational processes more efficient and improve the quality of specimens and data by optimizing these processes, relating to collection, processing, distribution of specimens and data (see *A3.2.2.3. Financial Sustainability* and *Section J2. Pilot Studies and Proof of Performance Studies*).
- Financial (*e.g.*, costs, funds, revenue): Repositories should secure financial stability by implementing an appropriate business model to include long-term funding and cost-recovery strategy (see *A3.2.2.2. Cost Recovery* and *A3.2.2.3. Financial Sustainability*).
- Social (*e.g.*, public/donor engagement): Repositories should increase social acceptability to acquire more trust and support from stakeholders, relating to ethical, legal, and social issues (ELSI), communication, and promotion (see *A5. Communication and Repository Promotion*).
- Environmental (*e.g.*, clean energy, sustainable harvesting): Repositories should acknowledge their environmental impacts (*i.e.*, carbon emissions related to digital hosting and processing capacity, cold storage, water requirements for cooling, and waste, *e.g.*, of equipment, personal protective equipment etc.) and have a well-considered strategy to conserve natural resources and protect global ecosystems to support health and wellbeing, now and in the future[9] (see *Sections C1.5. Environmental Impact and Biobanking* and *F4.11. Environmental Safety and Sustainability*).

There is overlap and interconnectedness between these components of sustainability. For example, the cost recovery fees are affected by operational efficiency, which impacts financial sustainability, and designing for energy efficiencies help lessen environmental impact and reduce operational costs. Therefore, the long-term sustainability of a repository is achieved through a balanced interplay between operational, financial, social, and environmental dimensions.

The repository should continuously evaluate and adjust based on stakeholder needs and with sustainability in mind so that the repository remains operative, effective, and competitive over its expected lifespan.

### A3.2.2. Financial Considerations

The cost for specimen collection, processing, storage, quality control, distribution, communication, and promotion can be considerable. Requirements for financial support may vary depending on the type of organization with which the repository is affiliated, the phases of the repository, and/or changes in marketing strategies and policies. The repository's receipt of public and/or private funding and the costs the repository incurs, including equipment replacement costs, should be considered when developing the financial strategy for the repository. The strategy for specimen and associated data collection and distribution and the overall financial strategy of the repository are often interconnected in the context of cost recovery (see *A3.2.2.2. Cost Recovery*). To ensure continued operations without compromising quality, a specific financial strategy should be developed for five years and beyond to estimate long-term costs and revenues (see *A3.2.2.3. Financial Sustainability*).

***BEST PRACTICE:*** A financial strategy should be created for the expected lifespan of a repository, including the life cycle of all specimens and data. The strategy should be reviewed on a regular basis and adjusted as needed.

#### A3.2.2.1. 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[10]. Where applicable, financial management representatives of the organization(s) with which the repository is affiliated should be included in the cost assessment exercise. Such projections can benefit from access to internal or outsourced financial expertise.

Critical costs to effectively initiate, develop, maintain, and close a repository should be considered from the outset. The actual costs to be considered will depend on the characteristics of the repository. For example, costs should be assessed for the following:

- Physical facilities (*e.g.*, lease, overhead, utilities such as gas, electricity, water).
- Personnel and administrative costs (*e.g.*, payroll including overtime, benefits, contract support, consultant fees, information technology [IT] services, professional development, training, conference attendance, publication fees, etc.). Costs for personnel development and specific education should be taken into account. Qualified technicians and scientists are vital for the sustainability and effectiveness of the repository. Personnel costs are often the largest ongoing expenditure in most repositories.
- Specimen processing and storage equipment purchase, qualification, maintenance, calibration, use, and repair and replacement (*e.g.*, freezers, cabinets, liquid handling machinery, cryo equipment, nucleic acid extractors, and quality control instruments such as automated electrophoresis solutions, spectrophotometer-based instruments, sequencer, microscope, as relevant).
- Supporting equipment (*e.g.*, monitoring equipment, barcode scanners, computers, office equipment, telecommunications).
- Inventory management software, licenses, maintenance, data processing, and cloud usage fees.
- Health and safety (H&S; *e.g.*, H&S training, disinfectants, biosafety cabinets, fume hoods, safety signage, environmental monitors; see *Section F. Health and Safety*).
- Consumables, reagents, and operating supplies (*e.g.*, buffers, reagents, chemicals including gasses, disposables, disinfectants, laboratory safety supplies, personal protective equipment, liquid nitrogen, diesel).
- Shipping supplies and courier fees.
- Service contracts for equipment maintenance and disaster recovery.
- Certification and/or accreditation or other quality management fees.
- Disposing of and/or transferring collections (see *A3.2.2.4. Relocation or Termination Costs*).
- Emergency and disaster preparedness and response planning (see *Section B2.3.1. Organizational Preparation and Action Planning*).

Evaluation of all costs related to work streams, systems, equipment, supplies, and ELSI should be completed prior to establishing fees for services provided. These costs should be reviewed on a regular basis and adjusted as needed.

***BEST PRACTICE:*** Prior to cost assessment, all work streams, systems, equipment, supplies, and services should be evaluated to enable cost recovery and to minimize waste.

***BEST PRACTICE:*** The operational life of infrastructure, including equipment depreciation, should be considered in preparation for timely replacement and expansion purchases.

### A3.2.2.2. Cost Recovery

Cost recovery refers to the ability to recover the costs of investments and/or to recoup the cost of any expense. In the context of a repository, cost recovery refers to reimbursement fees charged to end-users to compensate for non-appropriated source costs (costs that are not supported through an existing source) associated with the specimens and/or associated data and/or services provided. Even repositories that have most of their costs covered through external funding or other sources may wish to consider a nominal fee for services (other than distribution of specimens and/or data) to promote good stewardship and judicious use of resources. It may be appropriate for a repository to develop a proposed fee policy in consultation with the responsible financial function within the repository/parent organization and other stakeholder groups, (*e.g.*, potential end-users of the repository, and, where appropriate, participant advocates) to gain approval for use. Cost recovery should be justifiable for the activities performed, through a thorough analysis of the fee structure, and should be in line with any requirements from existing funding sources. Repositories may be perceived negatively if they are thought to be making a profit from donated specimens and data. The process for determining cost recovery fees and their application should be clear, understandable, accessible to stakeholders, and, above all, transparent to retain the trust of end-users.

A fee policy should additionally address the timely payment and non-payment of fees as well as disposal or redistribution of specimen collections that are no longer supported by funding (see *Section K4.2. Specimen and Data Transfer* and *K4.3. Specimen and Data Disposal*). These policies should be reviewed regularly and adjusted as needed. Use of a cost modeling tool may guide users in creating a more consistent user fee structure and promote transparency in user fee assessment[11-13].

Specimens and associated data and other services should be provided according to agreed-upon terms and with a documented quotation. Fees should be kept within a range that accommodates and permits optimal use of the repository.


ISBER Head Office: 1618 Station Street, Vancouver, BC, V6A 1B6, Canada
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***BEST PRACTICE:*** Cost recovery policies in line with existing ethical and legal requirements should be developed, periodically reviewed, and adjusted as needed to meet the needs of the repository and its stakeholders.

#### A3.2.2.3. Financial Sustainability

Financial sustainability represents a major challenge for the survival of a repository[14, 15]. The financial provisions can be divided in three parts:

- Costs and expenses: Start-up expenditures may include initial equipment purchases, inventory management and computers, inventory management systems, space planning, and construction. Operating expenditures may include employee payroll, consumables, energy costs, consultants, additional equipment purchases, equipment maintenance and replacement (see *Section H12. Equipment Maintenance, Repair, and Replacement*), training, transport, marketing and promotion (see *A5. Communication and Repository Promotion*), travel to conferences and meetings, and fees for qualification examinations for personnel.
- Funding: Funding may be obtained through grants from local, regional or governmental funding entities, funding by the host organization, philanthropic donations, and other private funding mechanisms. Regardless of funding sources, repository managers should prepare accurate, annual budgets to support orderly repository activities. Long-term funding strategy contributes to maintaining a sustainable operation of the repository.
- Revenue: Revenue depends on the financial model adopted by or imposed upon the repository. Revenue may be generated by providing different kinds of services such as collection, storage, transportation, processing, testing, experimental services, and consultancy service on a fee-for-service basis. Specific competencies (*i.e.*, ethical, cryotechnical, clinical, collection design) may become a source of revenue in terms of consultancy. A cost recovery approach that is in alignment with regulations, ethical frameworks, organizations policies, repository stakeholders, and social norms is one strategy used by some repositories to maintain a sustainable operation (see *A3.2.2.2. Cost Recovery*). However, financial sustainability is unlikely to be achieved with only a cost recovery model.

Even if fully funded as part of government/national strategic expenditure, the repository should develop appropriate cost optimization procedures to drive financial sustainability, especially when moving from start-up to active operation. Once all costs are defined, it might be possible to reduce costs by reviewing work processes and considering the ability to optimize workflows. The following cost saving measures can be considered for implementation[16]:

- Cooperate with other repositories or laboratories (within or external to the parent organization) and/or partner organization(s): Resource sharing can introduce economies of scale (common procurement), *e.g.,* personnel, equipment, space, or soft- and hardware for data management and/or services.
- Increase effectiveness and performance: A variety of options may be available for optimizing processes to perform the activities more quickly and efficiently while maintaining high precision and quality underpinning fitness for purpose. Routine activities should be examined to determine if automation might be incorporated to more rapidly process, store, and/or retrieve specimens (see *Section H4. Automated Storage Systems* and *H11. Automated Liquid-Handling Robotics*). While automation typically requires an increased initial expenditure and service contracts, the result may be a reduction in labor and facility costs over time. Alternatively, the possibility of offering a fee-for-service using in-house resources and expertise may provide new opportunities for revenue.
- Optimize personnel costs: Repositories may reallocate personnel from underutilized services to new or more highly used services. Repositories can also consider outsourcing of services to specialized service providers for shipping, facility and equipment maintenance, specimen collection and processing, etc.
- Reduce storage expenditures: Storage costs increase over the lifespan of a repository as non-consecutive and unoccupied spaces in freezer boxes increase due to accumulated retrievals for specimen distribution. The feasibility of storage consolidation should be periodically assessed to increase the storage efficiency. Additionally, specimens and collections may have a storage duration (per contract or consent) that requires disposal after a certain period of time. To improve storage efficiencies, a repository can establish policies and procedures for storage unit operation and maintenance to include criteria and methodology governing consolidation/removal/disposal of stored material.

***BEST PRACTICE:*** Repositories should have long-term projections for sustainability in addition to annual budget plans.

#### A3.2.2.4. Relocation or Termination Costs

Repositories should be prepared for unexpected circumstances such as a natural or financial disaster which may result in a shutdown of the repository. Contingency planning is one of the key components of long-term sustainability for all repositories. The repository may consider allocating some budget to a contingency fund for operating costs in the event of unexpected circumstances. A repository may be terminated for a number of reasons, such as termination of funding, depletion of specimens, and/or discontinuation of participation, natural disasters,[17] etc.

Repositories should have a defined termination plan or exit strategy as well as a budget for disposal or transfer of specimens and/or data, equipment, and facilities (see *Section K4. Transfer and Disposal*). The termination plan should provide information on the process and timing for closedown depending on the scenario (*e.g.*, shutdown, decommissioning, transfer, etc.). This plan should include personnel transition and communication with governing bodies and relevant stakeholders (*e.g.*, research ethics body, institutional review board, or oversight committee). Short-term funding may be needed to allow execution of the termination plan. When calculating termination costs, the following items may need to be taken into account:

- Professional disposal of specimens and/or data in line with applicable legislation and ethical authorization(s).
- Relocation and transfer of specimens and/or data, and equipment (*e.g.*, for specimen processing and storage) to third parties.
- Recycling or reuse of equipment, supplies, and facilities for other purposes (*e.g.*, education, development).
- Transferring experienced personnel to other repositories or institutions.
- Maintaining paper archives (informed consents, contractual agreements, research documentation, and accounting).

### A3.2.3. Components of a Business Plan

A business plan is fundamental to prepare for financial sustainability and eventually the success of the repository. A business plan may contain a repository profile section (*e.g.*, organizational structure, process, products, and services of repository), a market and communication section (*e.g.*, market, the potential end-users, competitors), and a sustainability section (*e.g.*, operational, financial, social, and environmental sustainability).

A repository business plan may include the following:

- **Cover and executive summary:** name of repository or projects, unique identifiers if available, a short document to summarize a full version of the plan.
- **Repository profile:** vision; mission; strategic objectives; organization data, including date of founding, number of employees, type of repository, types of products and services (specimen, data, services).
- **Business environment**: national and international trends in repositories, relevant current and future research projects and consortia, SWOT analysis (strengths, weakness, opportunities, and treats).
- **Management and governance:** organizational structure; management team/personnel; policies for access and sharing; key performance indicators; relevant ethical, legal, and social considerations (see *Section C. Ethical, Legal, and Social Implications*).
- **Financial planning:** business model, current and future costs, funding and revenues.
- **Communication and Promotion:** market analysis, stakeholder analysis and engagement, marketing and communication strategy to increase the trust of stakeholders (may also be part of operational plan) (see *A5. Communication and Repository Promotion*).
- **Risks and contingency planning:** potential risks and risk mitigation, disaster planning, business continuity planning (see *Sections B1. Risk Management* and *B2. Business Continuity Management*).
- **Exit and termination strategy**: legacy planning in the case of unexpected termination or in the event of a collection's utility end, resource constraints, stop funding, donor withdrawal, dissolution of the repository, etc. (see *Section K. Access, Distribution, Use, Transfer, and Disposal*).

The business plan should establish a process to proactively review whether the repository is meeting the needs of its stakeholders and end-users.

***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:*** If the repository type or services change, the business plan should be reviewed and updated to reflect the change in scope.



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## A4. REPOSITORY OPERATIONS

### A4.1. Repository Execution and Maintenance

The execution phase of a repository implements the strategy developed during the planning phase (see *A3.1. Repository Planning*) and may include any or all of the elements set out in *A1.2. Lifespan and Phases of a Repository*. For a new repository, the execution phase should include:

- Setting up facilities (see *Section G. Facilities*).
- Developing workflows and/or flowcharts to clearly map out key repository processes.
- Defining data management processes (see *Section I2. Data Management*).
- Selecting, purchasing, and or/or installing equipment (see *Section H. Storage and Processing Equipment*).
- Hiring or assigning personnel (see *A4.2. Repository Personnel*).
- Developing appropriate personnel training and assessment of competency (see *Section E. Training and Competency*).

This is also the phase when the repository's quality management and the related documentation that will underpin the different processes and activities, such as collection, characterization, processing, storage, and distribution of specimens is created (see *Section D3. Quality Planning*). Depending on the size, scope, or phase of a repository, these activities and documents may be formalized into an operations manual or a set of operational plans (see *A4.4. Operations Plans*).

Repositories track specimens and associated data that are under the control of the repository, generally from collection and receipt through to distribution or disposal. During the execution phase, the repository should implement an inventory or tracking system to keep track of the location of biological material and related data throughout this process, linking specimens and associated data (see *Section I3. Inventory Management Systems*).

During the maintenance (or monitoring) phase, a repository will manage the day-to-day activities as well as monitoring performance. This monitoring may focus on the following:

- Quality of specimens/data and services provided (see *Section D. Quality Management*).
- Adherence to processes and documenting non-conformities and corrective actions (see *Section D3. Quality Planning*).
- Tracking key performance indicators (KPIs) (see *Section D3.8.4. Key Performance Indicators*).
- Satisfaction of stakeholders (see *A5.2. Communication Strategy and Plan*, and *Section D3.8.3. External Feedback*).

During the execution or monitoring phases, the repository may identify changes that need to be made to the repository, services, personnel, financial model, or other essential areas. Repository personnel or governance (see *A2.1. Repository Governance*) should evaluate these in the context of the business plan for feasibility before initiating, planning, and executing these new activities. Furthermore, new activities should be documented through incorporation within the appropriate policies, procedures, and plans (both business and operational).

### A4.2. Repository Personnel

Repository personnel vary according to the needs of the organization and the services provided, and may be managerial, technical, administrative, and/or support personnel. Common roles needed to effectively manage and operate a repository are described here. However, the position titles and responsibilities may need to be adapted to meet the needs and resources of the repository. Personnel should be adequately trained and deemed competent to perform the tasks required by their job description and should follow all repository policies and applicable international, national/federal, regional, and local regulations (see *Section E. Training and Competency*) including for data privacy and how to handle confidential information. Additionally, repository personnel including leadership should disclose actual or potential conflicts of interest (see *Section C1.4.4. Impartiality*).

Repository personnel should be made aware that they might be handling and processing confidential and/or sensitive data, and should sign a confidentiality agreement or non-disclosure agreement (NDA); (see *Section I2.3.2. Data Privacy*). An NDA should be executed in such a way that when personnel cease to have a relationship with the repository (after leaving a job or discontinuing functional or advisory work with the repository), the terms and conditions of confidentiality continue to be binding on the signing party.

***BEST PRACTICE:*** An organizational structure with clear job descriptions with lines of reporting that reflects the full scope of the business plan should be documented for each role in the repository.

***BEST PRACTICE:*** Repository personnel should disclose actual or potential conflicts of interest.

***BEST PRACTICE:*** Confidentiality forms should be signed by repository personnel where the signee agrees to hold all confidential or proprietary information in confidence and that the information will be used only for authorized and documented purposes.

#### A4.2.1. Repository Oversight

The individual(s) with responsibility for day-to-day repository oversight (*e.g.*, Director, Head, Curator, Manager, top management) is referred to throughout this document as the Director. The Director should be qualified by expertise, training, and experience to direct and manage the scope of activities conducted by the repository, including those for quality management (see *Section D2. QM Roles and Responsibilities*).

While the concept and practice of leadership differs for different organizations, having appropriate and dedicated leadership is key to good operations to ensure the appropriate amount of time and effort is dedicated to the operation of the repository.

***BEST PRACTICE:*** Repository directors should have the appropriate amount of time and effort to dedicate to the operation of the repository.

##### A4.2.1.1. 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 (delegating operations accordingly). They are also often the signatory authority for the repository. Depending upon organizational structure of the repository, the Director serves as a liaison with key stakeholders and has other responsibilities related to ensuring:

- Adequate funding for operations (see *A3.2. Business Planning and Sustainability*).
- Operation within budget.
- All necessary authorizations (*e.g.*, ethics approval) are obtained prior to collection and maintained over the lifespan of the repository.
- A policy is in place for access to specimens and data stored in the repository and that requests for such resources are met in a timely fashion (see *Section K2. Access, Distribution, and Use*).
- Confidentiality of data.
- An effective quality management program is in place (see *Section D2. QM Roles and Responsibilities*).
- Education opportunities and career development for personnel.
- A training program is in place and implemented (see *Section E. Training and Competency*).
- Robust and auditable data retention (see *Section D3.2.2. Storage and Retention of Documented Information*).
- Health and safety (see *Section F. Health and Safety*).

##### A4.2.1.2. Personnel Supervision

The Director should oversee and approve the construction and maintenance of an organizational chart that delineates the functional relationships within the repository. Candidates for supervisory and technical roles should be approved by the Director. The Director should also approve and maintain job descriptions and document personnel 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 be responsible for developing and reviewing employee training programs (see *Section E. Training and Competency*). Specific qualifications and expertise may be necessary for personnel collecting and processing specimens and data according to different countries and areas. The director should enable technical personnel to maintain and update such qualifications and encourage attendance at academic conferences, workshops, and educational courses to acquire the necessary knowledge. They may also encourage and provide financial support to take qualification examinations to document biobanking ability.

##### A4.2.1.3. Quality Management

The Director and/or designee (*i.e.*, the Quality Manager) should ensure that a Quality Management (QM) program 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 (see *Section D2. QM Roles and Responsibilities*). The Director should require regular, documented, internal reviews or audits to ensure


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compliance with SOPs and regulations and to satisfy end-user requirements. If deviations from SOPs or quality indicators are identified, the Director should ensure that appropriate corrective action is undertaken successfully and documented (see *Section D3.8.1. Non-conformities* and *D3.8.2. Corrective and Preventive Actions*).

#### A4.2.2. Technical Personnel

The range of activities performed by repository technical personnel may include, but is not limited to: specimen and data collection, processing, quality control, retrieval for distribution, shipping and receiving, storage, data management, facility and equipment management, and health and safety. Technical personnel should have the necessary education, work experience, skills, and competence to guarantee that assigned tasks are executed in accordance with the implemented policies and specified SOPs. Technical personnel should strive to acquire the necessary specialized knowledge, and acquire and renew relevant qualifications, where feasible, (see *Section E. Training and Competency*). Duties should align to written job descriptions. Authority and reporting relationships for personnel should be clearly described.

***BEST PRACTICE:*** The repository should ensure that technical personnel are employed in a stable position (*e.g.*, job security and benefits, consistent working hours and salary, continuous development) to perform their required activities/tasks/duties.

### A4.3. Contracting Services and Consultants

When internal personnel resources are not sufficient to provide all necessary expertise, either during planning or as a repository evolves, a repository can seek assistance from qualified experts and consultants. Consultants should have documented experience in the area for which they are retained and have the capacity to deliver on the agreed scope of the work. Consultants might provide expertise in different areas, such as strategic planning; regulatory compliance (see *Section C1.2. Legal Implications*); facility design (see *Section G1. General Introduction to Facilities*); equipment selection; and decisions surrounding automation, SOP development, vendor selection, grants and cost recovery, contract management, and quality assurance. The repository may have contractual relationships with other organizations or service providers that provide access to facilities or services not available at its own location. Alternatives might include departments or functions within the parent organization.

The roles and responsibilities of any contracted service or consultancy should clearly be outlined by the Director or their designee. Due diligence (*e.g.*, evaluation of the contracting services, processes and procedures, facilities requirements, site visits, financial stability) should be carried out prior to implementing the contract. The Director, designee, and/or appropriate subject matter experts should evaluate contractors based on the agreed criteria. Once selected, the relationships, rights, and obligations of all parties should be established and clearly documented. Such documentation can include a contract, service agreement, or associated statement of work. Agreements should be reviewed based on the term of the agreement and renewed or updated, as necessary.

***BEST PRACTICE:*** Repositories should perform supplier evaluation for contracted services, and document and clearly communicate the scope of work with contracted parties.

### A4.4. Operations Plans

The repository should have plans in place to address the key elements for their planned and unexpected activities such as natural disasters. The plans should generally cover activities as listed in Table A3.

**Table A3.** Activities Typically Outlined in Operational Plans

| Topic | ISBER Best Practice Section location(s) of additional details |
|---|---|
| Repository operations, which may include workflows or process flowcharts | *A4.1. Repository Execution and Maintenance* |
| Personnel organization, roles, responsibilities, and accountabilities | *A4.2. Repository Personnel* |
| Risk and business continuity, disaster management including emergency preparedness and prevention | *B. Risk, Emergency, and Disaster Management* |
| Quality management | *D. Quality Management* |
| Training, competency assessment, and training evaluation | *E. Training and Competence* |
| Health and safety | *F. Health and Safety* |
| Equipment including purchase, maintenance, qualification, repair, and replacement | *H12. Equipment Maintenance, Repair, And Replacement* |
| Data management including documentation of specimen tracking and other software systems | *I2.1. Data Management Plan* |
| Specimen management including processes for collection, processing, access, distribution, transfer, and disposal | *J4. Collection Procedures*<br>*J5. Specimen Processing*<br>*J6. Receiving Specimens*<br>*K. Access, Distribution, Use, Transfer, and Disposal* |

Additional activities may include planning for expansion, automation, security (both physical and electronic), fire and accident prevention, environmental protection, etc. The extent of such plans may depend on the size and capability of the repository. These plans may be developed and retained as part of the repository's QM program (see *Section D3. Quality Planning*).

## A5. COMMUNICATION AND REPOSITORY PROMOTION

### A5.1. General

Communication is a key activity of a repository. Within the repository itself, communication between repository personnel and with institutional personnel, such as facilities, IT, and finance, is necessary to handle day-to-day operations and to respond to emergencies. Internal communication within the repository often occurs on a continuous basis to enable the repository to operate smoothly.

This section focuses on the importance of transparent and effective lines of communication with the repository's external stakeholders (see *A5.2.1. Identification and Engagement of Stakeholders*). Depending on the mission and purpose of the repository, there may be different reasons to communicate with stakeholders; however, a key goal is to establish trust. Transparency through communication is the basis of repository stakeholder trust, including but not limited to, that of donors/participants, researchers, sponsors, repository users, and the general public. Trust is foundational for donors and participants to contribute specimens and data, for researchers and end-users to use the repository's services, and for the public and funding bodies to understand and support the repository's efforts.

Repositories can also use communication strategies to promote their services, to maximize the use of their specimens and associated data and to share the impact of the repository (*e.g.*, publications and case studies). For example, this might include participation in existing biobanking directories or other similar types of platforms to increase the visibility of specimens and data to potential end users[18] (see *Sections I3.5. Virtual Platforms* and *K2. Access, Distribution, and Use*). Repository promotion may generate multiple benefits including increased cost recovery, recruitment of donors or participants, and recognition of the repository. Communication with sponsors or funding bodies may be needed to inform them of progress or to obtain additional support or funding, which contributes to the sustainability of the repository. Communication can also solicit objective feedback in order to improve the repository (see *Section D3.8.3. External Feedback*).



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How a repository communicates with its various stakeholders varies and should be tailored to the stakeholder group. How a message is communicated also depends on the purpose or content of the communication, the funding available to support the outreach, and the communication methods and media available to the repository.

The media used for communication can be print, video, or audio and be either static (*e.g.*, a website or article) or interactive (*e.g.*, a public presentation or focus group or a survey to solicit feedback). Examples of communication methods include:

- Repository or organization website.
- Newsletters.
- Webinars.
- Formal or informal written reports.
- Dashboards.
- Publications.
- Presentations.
- Podcasts.
- Social media.
- Focus groups.
- Facility tours or various public forums (*e.g.*, focus groups, seminars, etc.).

The repository should consider what is most engaging and appropriate for the message they want to send based on the purpose of communication to the specific stakeholder group.

The repository should identify their key stakeholders, the purpose for engaging with them, and the strategy or method for communicating in advance of initiating a communication campaign. This information should be part of an SOP, communication plan (see *A5.2.2. Communication Planning*), or other relevant document, and the cost of these activities should be accounted for in the repository's budget (see *A3.2.2. Financial Considerations*).

***BEST PRACTICE:*** Prior to the initiation of specimen and data collection, stakeholders should be engaged to evaluate communication strategies to ensure that expectations are satisfied and that transparency and trust can be firmly established. Stakeholders and repositories should have ongoing communication to ensure transparency and trust.

***BEST PRACTICE:*** Prior to the initiation of communications, the stakeholder(s) and the purpose of the communication should be clearly defined and the appropriate method of communicating this information should be considered.

## A5.2. Communication Strategy and Plan

A repository should consider the tone, language, and focus or theme of the messaging for communication planning. The following themes can be used to effectively promote the repository and its supportive role in research:

- Research collaborations that foster scientific advancements and knowledge sharing.
- Access to specimens and data to benefit research.
- Advancements, breakthroughs, or discoveries facilitated by the repository, focusing on the positive impact for participants/donors and society in general.

Featuring success stories or case studies of the research that has benefitted from access to the repository can help highlight insights gained while emphasizing repository accountability and transparency.

### A5.2.1. Identification and Engagement of Stakeholders

Stakeholders are individuals, groups, or organizations that are affected by or can affect a particular action undertaken by repositories. They may include donors/participants, end-users, research institutions, regulatory bodies, funding bodies, other repositories, the public, and others[19, 20]. There are numerous reasons to engage with stakeholders and the nature of the engagement, including the information shared, path of communication, and tone, is largely dependent on the nature of the stakeholder relationship.

The identification of stakeholders is not always easy. Stakeholders can be categorized by their involvement in the repository's business planning, operations, financial, or facilities support, etc. Stakeholders may include:

- **Donors/participants** who contribute specimens and data to the repository. Depending on the repository type and purpose, donor/participants may be informed about the following:
  - The purpose of collecting specimens (see *A2.1. Repository Planning*).
  - The risks in research using specimens (see *Section C2.2. Informed Consent Process*).

  - How to withdraw consent (see *Section C2.2.5. Withdrawal of Informed Consent*).
  - How and when specimens and/or data may be disposed of (see *Section K4.3. Specimen and Data Disposal*) or returned (see *Section C2.6. Return of Research Results*).
  - Policies for specimen and data use (see *Section K2.1. Access, Distribution, and Use Policy and Procedures*).
  - Opportunities and mechanisms for participation in governance, if applicable (see *A2. Repository Governance*).
  - Type(s) of participant engagement (see Section *C1.4.2. Community Engagement, Inclusions, Diverse Participation*).

- **End-users** are those who receive or use repository service(s). End-users may include researchers, organizations or departments within an organization, clinicians and primary care providers, and third-party laboratories. Prospective end-users of the specimens and associated data or other repository services should be informed of:

  - Specimen and/or data types available.
  - Contractual obligations or fees (see *A3.2.2.2. Cost Recovery*).
  - How to request specimens, data, and/or other services (see *Section K2. Access, Distribution, and Use*).
  - The limitations around specimens and/or data use (see *Section K2. Access, Distribution, and Use*).
  - Specimen and data quality (see *Section D. Quality Management*).
  - Services provided (see *A3.1.2. Services to be Provided*).
  - Acknowledgement requirements (see *Section K2.3. Acknowledging Repositories and Reporting Use*).

Feedback on specimen or service quality should also be part of communication with end users (see *Section D3.8.3. External Feedback*).

- **Funding organizations**, project partners, and industry communication may include sharing status of business performance or financials. This may be accomplished by setting KPIs (see *Section D3.8.4. Key Performance Indicators*) and communicating these through regular reports (*e.g.*, annual report). These stakeholders may also provide feedback on the KPIs or other measures of success. With the evaluations of these stakeholders in mind, the repository can identify areas for improvement of its business performance.
- Members of the **general public**. The public may be potential funders or donors/participants, including patient representatives and/or family members and the basis of a good relationship with them is social trust. Developing trust should involve active engagement, which may include disclosing business plans and operational status, thereby increasing transparency of its activities and constant improvement efforts see *Section C1.4.2. Community Engagement, Inclusion, Diverse Participation*).

Additional stakeholders/groups may include national, regional, or international associations or societies; press/media; governments; regulatory bodies; and legal consultants. How these stakeholders are communicated with should be determined by the needs and goals of that stakeholder group.

Additionally, the repository may wish to communicate with many stakeholder groups through a single method, such as a repository or organizational website. Consideration should be made to what information is presented on a website and the frequency of reviewing and updating this information. Much of the information relevant to the stakeholders listed above may be posted on a website, but a website may also include accreditations or certifications, an organizational chart, business or ethical compliance documents, event calendars, links to relevant regulatory documents, or best practices. All communications should be updated regularly. This is particularly important for websites as traffic to the website will decline if not regularly updated. The cost of regular updating should be factored into financial planning (see *A3.2.2.1. Identifying and Defining Costs*). Communications should be secure to protect privacy and not to disclose sensitive information.

***BEST PRACTICE:*** Information regarding the repository's operational and governance structures should be made available to stakeholders, as appropriate.

***BEST PRACTICE:*** The repository should identify stakeholders involved in the business and provide them with opportunities to participate in and contribute to the formulation of business, governance, and operational plans, as appropriate.

### A5.2.2. Communication Planning

A repository should have a formal plan for communicating to external stakeholders. This plan may be embedded in the business plan or as a standalone operational plan. The scope, level of detail, and formality of the plan should



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align with the needs of the repository (and stakeholders), the stated goals and purpose, and the current life phase of the repository. Any communication plans should be reviewed and updated as needed to support the ethical and business needs of the repository and should include:

- A list of the repository's key stakeholders.
- The information to be communicated to each category of stakeholders.
- Specific plans for promoting repository services to potential end-users.
- Gathering feedback from appropriate stakeholders (see *Section D3.8.3. External Feedback*).

The communication plan should entail how information will be communicated. For example, the plan may outline what information will be provided on the repository or organization website(s), in pamphlets or newsletters, presented at seminars or meetings etc. It may also include the frequency of reviewing and updating communication. A specific annual communication strategy may specify meetings, events, *e.g.,* for participants, end-users, and conferences in which the repository should participate or host, as well as articles to submit for peer review or other publication. The cost to execute the communication plans should be evaluated and budgeted for.

***BEST PRACTICE:*** A repository should have a plan for communicating with stakeholders that aligns with its stated goals and purpose and fits the needs of the repository type and phase.

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# SECTION B: RISK, EMERGENCY, AND DISASTER MANAGEMENT

## B1. RISK MANAGEMENT

### B1.1. General Introduction to Risk Management

Risk management is a set of structured processes and practices a repository can apply to identify or detect, evaluate, manage, and control inherent risks to increase the likelihood of successfully achieving the repository objectives. To be effective, a repository should apply a comprehensive approach to risk management for all phases of repository operations (see *Section A1.2. Lifespan and Phases of a Repository*). This includes initial business planning (see *Section A3.2. Business Planning and Sustainability*), ongoing routine activities (see *Section D3.1. Quality Manual*), and when considering strategic and/or operational changes.

Controlling risk is an essential part of responsible and effective risk management and helps to prevent the realization of a risk. Risks controls are measures and strategies put in place to reduce the likelihood of negative outcomes and to minimize the impact of adverse effects. Risk controls include avoidance, transference, mitigation, and acceptance. Applying controls can have wide-reaching benefits including safeguarding resources (*e.g.*, financial, digital, physical, or intellectual), maintaining operational activities, safety, sustainability, as well as reputation protection. A repository should develop strategies to determine and address risk priorities needing additional focus on resources. The strategies should be customized according to the size of the organization. Ultimately, risk management should both inform and support approaches for business continuity (see *B2. Business Continuity Management*). International standards can act as a resource for additional information[1,2].

### B1.2. Risk Management Process

Fundamentally, the risk management process involves at least four steps: i) Identify, ii) assess, iii) treat/control, and iv) monitor and review. All steps are applied in an ongoing, cyclic practice as shown in Figure B1. Fundamental risk management process. Additional considerations and more complex process models are sometimes used by larger or more complex organizations to meet more complex needs for risk management mapping[3,4].


**Figure B1.** Fundamental Risk Management Process

1. Identify risks (*i.e.*, potential areas of concern or tension).
2. Assess probability of occurrence and extent or severity of consequences.
3. Determine measures to treat, or control risks.
4. Monitor the outcome of measures taken and continued or new risks. Review and make changes as needed.



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### B1.3. Identification of Risks

Risk identification is the process of finding, recognizing and documenting risks. There are a number of ways to help identity risks. Risks pertaining to specific activity areas are indicated throughout different sections of this Best Practices document (*e.g., F4.1. Biorisk Management*). Processes or tools, such as analysis of data gathered, lessons learned or SWOT analysis (used to determine and manage strengths, weaknesses, opportunities, and threats) can be used to identify risks[5]. Business practices such as use of key performance indicators (KPIs; see *Section D3.8.4. Key Performance Indicators*) to meet stakeholder expectations can also assist to recognize risks. High-level categories and commonly identified repository risk examples are available in literature[6-13].

A list of selected broad risk categories is provided below for guidance:

**External risk categories:**

- Natural disasters:
  - Biological, *e.g.*, epidemic, contamination, toxic mold.
  - Geophysical, *e.g.*, volcanic eruption, earthquake.
  - Hydrological, *e.g.*, flood, tsunami.
  - Climatological, *e.g.*, wildfire, drought.
- Political, *e.g.*, non-functioning government, changes in exchequer funding.
- External agent, *e.g.*, war, (bio)terrorism, cybercrime.
- Public health risks, *e.g.*, epidemic, pandemic.
- Climate change, *e.g.*, temperature, humidity, climate change controls.

**Internal risk categories:**

- Strategic risk:
  - Economic sustainability.
  - Regulatory or governance failure/shutdown.
- Stakeholder risks:
  - Participant / donors, contribution.
  - Affiliated organizations, partners.
  - Research community.
- Process-related risks:
  - Invalid/no consent.
  - Data collection, storage error.
  - Failure to adhere to procedures.
  - Specimen or data mismanagement.
- Infrastructural risk (including technical and personnel):
  - Safety risks.
  - Power failure/equipment failure.
  - Supply chain disruption.
  - Cold chain (courier) failures.
  - Skills retention/continuity of staffing.
  - Human resources/repository personnel.
  - Facility/equipment damage, *e.g.*, due to fire, flood, sabotage.
  - Security of access to facility, equipment (hardware and software), and database.
  - Data breach or loss.
  - Building-related, *e.g.*, specimen storage environment below grade (*e.g.*, basement).

The repository should develop a risk register listing all the identified risks in order of importance.

***BEST PRACTICE:*** Repositories should develop a risk management policy. This policy should outline a risk management framework appropriate to the repository's activities and resources, and the processes the repository uses to identify, assess, control, and monitor risks during the lifetime of the repository. All repository personnel should be familiar with the risk management policy.

### B1.4. Assessment, Control, and Monitoring of Risks

An organization should assess each identified risk by considering the criticality of the activities and potential consequences linked to that risk. Guidance for (biosafety) risk assessment as well as risk assessment templates are provided within the World Health Organization (WHO) Laboratory biosafety manual, fourth edition[9], (see *Section F4.1.1. Biosafety*). The elements of quality management (see *Section D3. Quality Planning*) should serve as the benchmark by which risk is measured[14].

For existing repositories, many risks may already have one or more controls in place, *e.g.*, temperature monitoring and alarm-alert devices used for assessing storage of temperature-sensitive specimens. Assessing each risk using a risk matrix that evaluates impact versus likelihood, provides a structured risk rating system for intercomparison of risks (see Figure B2. Example Risk Matrix Tool to Determine Mitigation Strategies and Intercomparison of Risks). Ratings can be used to determine risks that merit more extensive mitigation, versus those risks that can be accepted within the repository's risk tolerance.

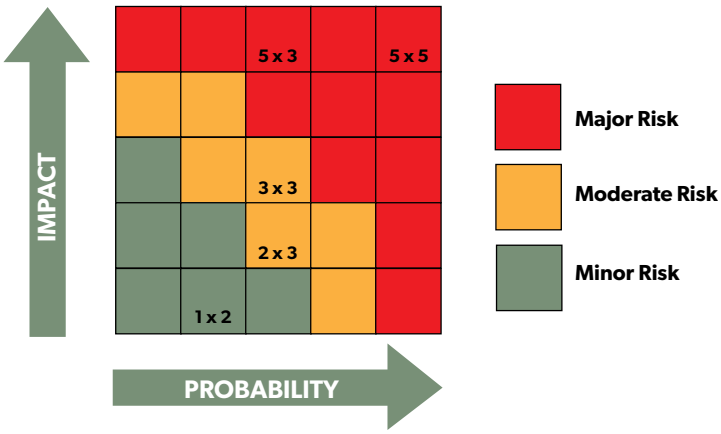


**Figure B2.** Example Risk Matrix Tool to Determine Mitigation Strategies and Intercomparison of Risks

Documenting the risk assessment and control measures (mitigations) is commonly managed through a risk assessment table. This should account for:

- Risks and mitigations.
- Risk assessment information (*i.e.*, rating based on probability of occurrence and impact level).
- Accountability (*i.e.*, person(s) accountable for managing the risk).

To be effective, risk management should be an ongoing practice for continued consideration and re-evaluation of existing and newly identified risks. On an ongoing basis, assessing risk and developing an understanding of existing controls can help to inform priorities and direct resources to better control the higher-level risks.

***BEST PRACTICE:*** The repository should identify relevant risks, assess those risks using a defined evaluation/rating method, and assess effectiveness of mitigations in place on a defined periodic basis, *e.g.*, using a risk register and risk matrix.

***BEST PRACTICE:*** The repository should identify and assign responsibilities for risk management and mitigation activities to personnel both within and outside the repository (as applicable).

Examples of common repository risk categories and mitigations are listed in Table B1. Repository Risk Categories and Proposed Mitigations. The table is not exhaustive and further risks are addressed in literature[4-9].



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**Table B1.** Repository Risk Categories and Proposed Mitigations

| Risk Category | Common Repository Risk | Example Mitigation | In-document Section References |
|---|---|---|---|
| Economic | Financial sustainability | Secure funding (*e.g.*, grants)<br>Diversify income streams<br>Implement business plan<br>Instigate cost-recovery plan | *A3. Repository and Business Planning* |
| Infrastructure (technical) | Supply chain disruption | Identify multiple material/supply sources, *e.g.*, find suppliers and distributors close to repository site(s) to reduce times for product development and delivery<br>Anticipate supply use rate and review ordering time frame<br>Build buffers for inventory<br>Consider stockpiling or preparing prior to periods of high risk (*e.g.*, top-up fuel for backup power generators prior to storm season) | *G. Facilities* |
| | Cold-storage unit (*e.g.*, storage equipment breakdown) | Alarm-alert monitoring system | *G. Facilities* |
| | | Implement safeguarding mechanisms to prevent inadvertent disarming of the alarm/alert system | *D3.1. Quality Manual* |
| | | Monitor storage temperature | *J3.6. Specimen Integrity Monitoring*<br>*H3.1. Monitoring Mechanical Storage Parameters*<br>*H2.2. Monitoring Liquid Nitrogen Storage Parameters* |
| | | Backup storage<br>Backup power, *e.g.*, through use of a generator | *H9. Backup Storage Capacity* |
| | | On-call paging system to contact personnel | *E. Training and Competency* |
| | | Divide specimen collections across different storage units and locations | *K4.2. Specimen and Data Transfer* |
| | Poor inventory management | Select the critical limits for storage unit(s), *e.g.*, temperature and time | *H2.1. Liquid Nitrogen Storage Equipment Types*<br>*H3.1. Monitoring Mechanical Storage Parameters* |
| | | Minimize temperature excursions, *e.g.*, due to door opening and specimen retrieval practices | *J7.2. Specimen Retrieval* |
| | | Monitor critical parameters such as temperature and time with the assistance of an alarm-alert system | *J3.6. Specimen Integrity Monitoring* |
| | | Manage specimen inventory | *J8. Specimen Inventory Management* |

| Risk Category | Common Repository Risk | Example Mitigation | In-document Section References |
|---|---|---|---|
| Infrastructure (technical) | Poor inventory management | Perform data management | *I2. Data Management*<br>*I3. Information Management System* |
| | Cold chain courier failures | Use specialist cold chain courier | *L. Packaging and Shipping* |
| | | Use of the appropriate cold chain equipment<br>Maintain list of alternate suppliers<br>Use environmental awareness to avoid potential of poor weather or other factors<br>Consider courier insurance, if provided | *I3.15. Data Associated with Shipments* |
| | Data breach or loss | Use of a data management plan, including data security, privacy, and data back-up | *I2. Data Management* |
| | | Ensure information management policies and procedures training and competency assessment are sufficiently addressed | *E. Training and Competency* |
| | Inadequate verification/ validation/ qualification | Evaluation of equipment, processes<br>Evaluate processes and all relevant components | *D3.6. Validation, Verification, and Qualification* |
| | | Ensure service agreements are sufficient and in place and renewed as necessary | *A4.3. Contracting Services and Consultants* |
| | | Maintain, repair, and/ or replace equipment, as appropriate | *H12. Equipment, Maintenance, Repair, and Replacement* |
| Infrastructure (repository personnel) | Loss of competent personnel<br>Poor performance/ repeated failures | Cross-skilling of personnel where possible<br>Partner with other institutions and organizations<br>Avail of professional development opportunities, *e.g.*, QBRS,<br>SOPs, (re)training and competency programs in place<br>Employ succession planning<br>Offer security in job status | *E. Training and Competency* |
| Infrastructure (biosafety) | Biological exposure | Ensure Bloodborne Pathogen Exposure Control Plan, biospecimen handling policies and procedures (*e.g.*, Biological Safety Cabinet/Biosafety Level 2 requirements)15 are in place and adequate | *F. Health and Safety* |
| Participant/ donor/provider | Breach of privacy and/or data security | Safeguard digital information, including access control | *C. Ethics, Legal, Social Implications* |
| | | Use confidentiality agreements, and operate a culture of confidentiality | *I2.3. Data Security and Privacy* |



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| Risk Category | Common Repository Risk | Example Mitigation | In-document Section References |
|---|---|---|---|
| Organizational | Breakdown in governance or regulatory oversight | Ensure governance oversight is in place | *A2. Repository Governance* |
| | | Create a culture of compliance | *C1.2. Legal Implications* |
| | | Conduct appropriate due diligence for adhering to regulations | *C1.4.1. Benefit sharing* |
| | | Use of agreements (*e.g.*, material transfer agreements [MTAs]) | *K3. Transfer Agreements* |
| Reputational | Any/all of the above | Monitor and re-assess risks and mitigation measures/controls regularly<br>Plan appropriate communication with critical stakeholders | *A5. Communication and Repository Promotion* |

## B2. BUSINESS CONTINUITY MANAGEMENT

### B2.1. General Introduction to Business Continuity Management

Business continuity management refers to processes involved in building an organization's resilience. This is done by providing guidance to proactively prepare for risks, as well as a framework to follow when reacting or responding to unplanned or undesired events in a manner that safeguards the interests of its key stakeholders, reputation, brand, and value-creating activities. It includes response strategies for identified or potential risks (threats) to an organization and consideration of the impacts to business operations should those threats eventuate.

### B2.2. Business Continuity Plan

A business continuity plan details the critical information and procedures that guide organizations to respond, recover and resume, and restore to a predefined level of operation following a disruption. A repository-specific business continuity plan should consider the organization context of the repository, leadership, planning, support and resources, operational planning, and evaluation components. This section elaborates repository-specific considerations to assist plan development.

Disruptions or 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 activities. The type and duration of an emergency or disaster may depend on the geographic location at which the repository is located.

Repositories should have a written business continuity plan that addresses emergency and disaster preparedness, response, and recovery for a wide variety of events. Risks with the highest likelihood and impact should be included in the plan. The plan should be aligned to the organization's objectives, should have management support for the necessary authorizations, and should be tested periodically (*e.g.*, at least annually) to ensure that all personnel are trained and deemed competent and that the plan meets the anticipated needs (see *Section E. Training and Competency*). The repository's parent organization may already have a business continuity plan in place, and the repository should align its plans with those. These plans should be accessible to all personnel. Additionally, repositories should consider local, national, and international resources as relevant for emergency response to a regional or global event, such as the WHO[12] and/or Centers of Disease Control (CDC)[13].

***BEST PRACTICE:*** Repositories should have a business continuity plan addressing emergency and disaster preparedness, response, and recovery. The plan should identify organizational risks and repository operational priorities, and be specific to the repository's operations, personnel, and anticipated or available resources.

### B2.3. Emergency and Disaster Preparedness and Response Planning

When developing an emergency and disaster preparedness and response plan, a number of steps or stages should be taken into consideration, as shown in Figure B3. Emergency and Disaster Management Cycle. This management cycle establishes the framework for creating, reviewing, or updating emergency and disaster preparedness and response.

In general, prior to an event taking place, the repository should prepare for any type of emergency or disaster by identifying (*i.e.*, *Identification* stage), preventing, or minimizing damages from that event through the risk management process (*i.e.*, *Preparation stage*) (see *B1.2. Risk Management Process*).

Once an event occurs, the first phase is the response (*i.e.*, *Response* stage). This includes the immediate reaction to the event and containment of impacts. Emergency and disaster recovery is the determination of the continuation of the activities of a repository on some level, either partially (*i.e.*, critical activities only) or in total (*i.e.*, *Recovery* stage). The last phase of the cycle includes reviewing the plan and addressing lessons learned in order to mitigate the impacts during future events (*i.e.*, *Mitigation* stage).


**Figure B3**. Emergency and Disaster Management Cycle

***BEST PRACTICE:*** Emergency and disaster preparedness and response plan(s) should include the identification, preparation, response, recovery, and mitigation of an event. This should include the highest priority scenarios (high likelihood and/or high negative impact) and should be documented in the plan and conveyed to all personnel.

### B2.3.1. Organizational Preparation and Action Planning

The following elements are key parts approaching preparation and action planning:

- **Emergency and Disaster Response Team Development**

The Response Team oversees the implementation and execution of the plan and members might include the repository Director, collection stakeholders, health and safety representatives, facility engineers, and building directors. Identifying the roles and responsibilities of each team member will establish the incident command/leadership reporting structure. The team and corresponding roles and responsibilities might be different for each type of event and some of the team members may not be available due to personal impacts of the event, *e.g.*, due to illness, injury, fatigue, or post-traumatic stress. The repository should identify key individuals to serve as on-call or be able to respond to an event at the repository. Leave and vacation schedules should be maintained and monitored to ensure that essential responsibilities are covered should key individuals be unavailable. Emergency contact numbers should be posted in prominent locations in the repository and should be accessible at all times by on-call and emergency personnel. The contact information should be reviewed on a regular basis to ensure that the information contained therein is current.

A skeleton response team or continuity team (those personnel who are most-needed in alignment to critical roles) should be established if applicable, and include essential authorizations to enable performance of critical roles under restrictive conditions (*i.e.*, access to the locations relevant to enable response to the event or to allow continuation of critical activities).


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- **Define the Scope of Resources**

Define the scope of the resources available according to the type and size of the repository. If the facility where the repository is located is leased or shared with other institutions/partners, ensure someone with the necessary authority is part of the emergency and disaster response team, and if access is restricted during an event, that the response/continuity team members can gain safe access to the repository.

- **Assess the Budget**

The budget requirements should be considered. Assess the operating budget that is part of the business continuity plan before an event occurs and consider what additional emergency funds might be needed to continue critical operations or to resume operations once recovery has occurred. If possible, ensure that emergency sources of funding are available, internally or externally (see *Section A3.2.2. Financial Considerations*).

### B2.3.2. Physical Preparedness

The following elements are key parts approaching physical preparedness:

- **Facility and Data Infrastructure**

The age, design, and structure of the building should be considered when determining how to mitigate some of the risks that are identified. For instance, assess whether the building is earthquake-proof if located in an earthquake zone, or if it is an older structure determine its compliance with current building codes. Is the building considered fire resistant should a fire occur? This information can help determine what measures should be taken into account to reduce the risk should an emergency or disaster occur. Identifying additional building hazards and appropriate control measures can help mitigate specific risks. Hazards such as power requirements for the repository, including emergency power and uninterrupted power supply back-up systems; heating, ventilation, and air conditioning equipment; fire detection and suppression; and security and access to the building, should be considered (see *Section G. Facilities*). A specific data management plan that details data response planning including data backup may form part of the overall emergency and disaster response and preparedness plan (see *Sections I2.1. Data Management Plans*, and *I3.14. Data and Systems Backup and Disaster Recovery*).

- **Safety and Security**

After identifying the roles of each team member, personnel orientation and training should be conducted (see *Section E. Training and Competency*), considering both safety and the security systems in place at the repository. Training should detail personnel roles to ensure each individual is aware of their role in the plan. In addition, emergency services contact information should be included in the plan and posted so that the entire team is aware of how to contact someone should it be needed. Contact information to services such as the fire department, police department, sanitation department, environmental protection, and local hospitals should be included.

- **Operational and Safety Toolkits**

Operational and safety toolkits, both general supplies and emergency supplies, should be assembled and available at all times should an emergency or disaster occur. The entire team should have access to the kits.

### B2.3.3. Procedural and Operational Preparedness

The key elements of procedural and operational preparedness include:

- **Resource Planning:** Development of resource plans for day-to-day activities (*e.g.*, standard operating procedures, forms, inventories already in place) as well as additional plans in case of an emergency or disaster (*i.e.*, safety/security, information systems, communication, contingency) can ensure that the organization is ready to respond and adapt to an event. A key resource is the availability of backup systems, including:
  - » Backup power (see *Section G6.1. Backup Power Supply*).
  - » Backup for specimen storage (see *Section H9. Backup Storage Capacity*).
  - » Backup of data (see *Section I3.14. Data and Systems Backup and Disaster Recovery*).
- **Defining Critical Operations:** The critical operations of the repository are those core activities without which the integrity of essential resources such as specimens and/or associated data will be negatively impacted. A repository should identify a list of critical stored collections and core activities and prioritize them to guide decision making for personnel that are responding independently or within a (defined) time or other constraints, *e.g.*, minimal liquid nitrogen ($LN_2$) supply or non-functioning mechanical freezers. Critical activities include, but may not be limited to:

  - Personnel health and safety.
  - High value or irreplaceable specimens and/or data.
  - Facility access.
  - Remote and offline access to critical systems, including documentation and data.
  - Critical operations/services to stakeholders.
  - Critical storage and monitoring.
  - Communication platform/tools.
  - Supply chain management.

- **Emergency Response Testing:** Disaster and emergency response tests/drills are one way of measuring the state of readiness and testing the effectiveness of an emergency and disaster response plan. The repository should document such tests and identify what went wrong and how gaps and issues should be revised or addressed to optimize future responses. Where possible, for large-scale emergency and disaster preparedness planning, participating in inter-organizational training exercises can strengthen communication and cooperation required for collaborative incident responses. Cross-training and maintaining an agile and multi-skilled workforce can strengthen the organization's capacity to adapt during and following an event (see *Section E1.1. Resources for Training and Competency*).

  Repositories can establish agreements with partner organizations for temporary storage of specimens in case of an event causing closure of the repository. An action plan for planned and unplanned transfer of collections should be established and tested if possible (see *Section K4.2. Specimen and Data Transfer*).

***BEST PRACTICE:*** The Director or designate should communicate with local power providers and all emergency services to request that the repository is placed on a list of high-priority users for power restoration following an emergency or disaster. This will ensure that local emergency services are aware of any potential environmental, chemical, flammable, or biological concerns if the emergency affects the facility.

***BEST PRACTICE:*** If repository inventory management systems (IMS) are housed on a server located away from the repository, consideration should be given to storing electronic inventory records on site to ensure that records are accessible during an emergency or disaster.

***BEST PRACTICE:*** Processes for notifying security and checking environmental monitoring systems should be verified on a routine basis. Where practicable, emergencies should be simulated to ensure proper follow-through for the established emergency and disaster response plan.

***BEST PRACTICE:*** Repositories should ensure that relationships with key stakeholders, such as emergency and response personnel (*e.g.*, firefighters) and repository suppliers, are in place to ensure appropriate responses to potential emergencies, *e.g.*, chemical fire, low-oxygen environment, critical supplies (personnel protective equipment/generator fuel) replenishment.

***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.

### B2.3.4. Communication and Coordinated Responses

Clear communication as well as having roles and responsibilities defined in a repository emergency and disaster preparedness plan can greatly assist the effectiveness of the response, particularly when responders are under unexpected stress or pressure. Repositories should consider establishing reporting and communication systems (see *Section A5. Communication and Repository Promotion*), including:

- Maintaining current list of contacts including for on-call system.
  - Communication platforms to be used.
  - Consideration of alternate communication modalities, *e.g.,* radios when telephone wires or cell phone towers are damaged during a natural disaster (*i.e.*, hurricane, earthquake); drones for surveying damage to isolated areas; other emerging technologies.
  - Personnel responsible for sending emergency notification/agreed statements.
  - Personnel that employees can contact to update on their situation and availability to assist.
  - Personnel responsible for informing stakeholders and managing public and media.
  - Testing of emergency notification system(s).
- Keeping an incident event log (and use of log to assist reviewing plans post-incident).
- Activities to be undertaken when emergency notification is received.


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- Change management practices, particularly for extended or permanent changes as a result of an emergency or disaster.

Repositories should have a checklist of activities for on-call personnel to follow during an emergency. On-call personnel should be familiar with the location and operation of certain key equipment and controls (*i.e.*, circuit boards, emergency equipment, $LN_2$ handling) that may need to be used during an emergency or disaster. Contact information (telephone numbers, etc.) for organization or external professional assistance (*e.g.*, engineering or facilities personnel, power companies, fuel supply companies, transportation services) should be clearly posted in the repository and in accompanying administrative areas.

***BEST PRACTICE:*** Repository emergency response personnel should be fully trained and deemed competent on all critical procedures and equipment for both emergency response and ongoing operations.

***BEST PRACTICE:*** The on-call system should be routinely tested to ensure it is functioning properly.

### B2.4. Organization Recovery Planning and Evaluation

The recovery planning process involves performing or reviewing the business impact analysis to determine critical business activities and priorities in order to return and resume to normal (or the accepted level of) operations. The goal of the recovery plan is to outline actions to be taken to recover from an event in order to minimize disruption and recovery time. All personnel should be provided with information and updates on the recovery efforts and planning, as well as be facilitated to provide feedback or report identified or potential barriers to the planning team. Depending on the emergency or disaster, considerations may include:

- What needs to be done before normal operations can resume.
- Resources availability.
- Priorities.
- Stakeholder considerations or barriers that may impact the plan (*e.g.*, cold-chain supply delay, approval to return onsite).
- Procedures to get collections back, if necessary.
- Checking/verifying facilities or equipment before moving specimens back (*e.g.*, re-performing validation/verification of cold storage unit(s) prior to returning content (see *Section D3.6. Validation, Verification, and Qualification*).

Post recovery, repositories should monitor and review the risk management and emergency and disaster response plan to identify what worked well and what did not work and remaining gaps. The plan and resources should be updated as needed.

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# SECTION C: ETHICAL, LEGAL, AND SOCIAL IMPLICATIONS

## C1. GENERAL ETHICAL, LEGAL AND SOCIAL IMPLICATIONS FOR REPOSITORIES

The collection, storage, processing, distribution, use, and disposal of biological specimens and associated data has many ethical, legal, and social implications (ELSI). ELSI pertains to virtually all types of repositories including those involving specimens and data for humans, animals, plants, and microorganisms. Furthermore, elements of ELSI should be considered in the design, planning, participant recruitment, specimen/data collection, storage, access, sharing and distribution, and return of research results from repositories.

Repositories should uphold key values related to research integrity, including transparency, accountability, and impartiality. These values are demonstrated by acting with honesty in generating and reporting data and methodology, as well as in interacting with donors, research participants, sponsors, funding agencies, and other stakeholders. They are also demonstrated by ensuring accuracy and avoiding bias in research methodology and adhering to relevant regulations and guidelines and commonly accepted professional codes or norms. Acting with integrity involves using resources responsibly and avoiding waste.

Repositories serve as custodians of the specimens they collect, process, store and distribute (see *Section A1.1. Types of Repositories*). Individuals who donate specimens for research expect that repositories will handle specimens and associated data in ways that are ethically, culturally, and scientifically sound. Building and maintaining the trust of participants/donors/providers, funding agencies and sponsors, end-users, and the public is important to ensure continued participation in and funding of research and ultimately repository sustainability. Repositories should be honest and transparent by sharing information about their operations with donors/participants throughout the repository lifespan (see *Section A5.2. Communication Strategy and Plan*). Transparent communication is key for activities including the informed consent process (see *C2.2. Informed Consent Process*), repository governance and oversight processes and procedures (see *Section A2. Repository Governance*), and in sharing individual and/or general research results (see *C2.6. Return of Research Results*).

Many of the ELSI discussed throughout this section apply broadly to human, animal, plant, and microbial specimens. Additional or unique considerations for collections in specific domains are discussed separately. Repositories should consider that multiple ELSI may apply to complex specimens involving multiple species, (*e.g.*, microbiome specimens, environmental dust or debris) and may differ depending on jurisdiction and the species involved.

### C1.1. Ethical Principles and Recommendations

Ethics refers to the branch of knowledge that deals with moral principles. Key ethical issues in research involving humans are found in a number of documents including the Declaration of Helsinki, first developed by the World Medical Association in 1964 and revised most recently in 2013[1]. Three basic principles – Respect for Persons, Beneficence, and Justice – have been widely adopted to guide the ethical conduct of research involving humans[2].

- **Respect for Persons** recognizes the intrinsic value of human beings. It includes the requirement to acknowledge individual autonomy and to protect those with diminished autonomy. This principle requires that participants be free to engage with research voluntarily and with adequate information.
- The principle of **Beneficence** involves seeking to maximize potential benefits while minimizing risks of inflicting harm (either intentionally or unintentionally).
- The principle of **Justice** requires that the burdens and benefits of research are distributed fairly. In fair distribution, no segment of the participant population is unduly burdened by the harms of research or denied the benefits of the knowledge generated from it.

Furthermore, understanding the ethical implications for communities impacted by repository activities (including participation) is expanding and contributes additional fundamental ethical expectations.

- **Community Ethics** involves recognizing and incorporating the religious and cultural norms and values of any potential participating communities[3]. For example:
  - Some cultures prioritize communal rights in consideration of an individual's connections to and decision-making traditions with families, friends, and community, in contrast to a sole focus on individual autonomy[4].
  - Community-focused perspectives may expand to the environment and areas of specific religious or cultural significance.



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Ethical principles and recommendations for best practices are continually evolving through the ongoing efforts of regional and international groups formed for the purpose of advancing ethical practices in science and social disciplines. While not a comprehensive listing, the following table (Table C1.) presents a sampling of documents that provide guidance and obligations for ethical conduct.

**Table C1:** Documents That Provide Guidance and Obligations for Ethical Conduct

| **Documents for ethical principles for research involving humans** |
|---|
| • World Medical Association (WMA) Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects[1] |
| • WMA Declaration of Taipei on Ethical Considerations Regarding Health Databases and Biobanks[5] |
| • Organization for Economic Cooperation and Development (OECD) Guidelines on Human Biobanks and Genetic Research Databases[6] |
| • Council for International Organizations of Medical Sciences (CIOMS) International Guidelines for Health-Related Research Involving Humans[3] |
| • Council of Europe Recommendation CM/Rec(2016)6 of the Committee of Ministers to member States on research on biological materials of human origin[7] |
| • Ethics and Governance Framework for Best Practice in Genomic Research and Biobanking in Africa[8] |
| • United States Department of Health & Human Services - The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research[2] |
| • Australian Government National Health and Medical Research Council National Statement on Ethical Conduct in Human Research[9] |
| **Regulations and treaties for responsible custodianship for plant, animal, microbial, and other species** |
| • Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity (CBD)[10] |
| • International Treaty on Plant Genetic Resources for Food and Agriculture[11] |
| • Cartagena Protocol on Biosafety to the Convention on Biological Diversity[12] |
| • Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES)[13] |
| • Agreement under the United Nations Convention on the Law of the Sea on the conservation and sustainable use of marine biological diversity of areas beyond national jurisdiction (BBNJ)[14] |

Based on the ethical principles and concepts developed by these organizations and others, recommendations for repositories include:

- The repository's purpose and mission (see *Section A1.1. Types of Repositories*) should contribute to the benefit of society (see *C1.4.1. Benefit Sharing*).
- Repositories should use strategies to demonstrate trustworthiness and establish and maintain the trust of all stakeholders:
  - Repositories should act with honesty and integrity and be accountable for their actions and operations.
  - Repositories should strive to be transparent through stakeholder communication regarding the nature, purpose, and objectives of the repository, and policies related to specimen and data handling and management (see *Section A5. Communication and Repository Promotion*).
  - Repositories should be sensitive to the values and culture of the communities involved or potentially impacted by the repository activities.
  - Repositories should engage participants and communities for the purpose of establishing and maintaining trust (see *C1.4.2. Community Engagement, Inclusion, Diverse Participation*, and *C1.4.3. Vulnerable Participants*). Engagement is recommended early[15] and should continue throughout the life cycle of the specimens and data, where practicable (see *Section J1. General Introduction to Specimen Collection, Processing, Receiving, and Retrieval* for information on the life cycle).
- Collections should be carefully planned and conducted by trained personnel with appropriate ethical expertise (see *Section E. Training and Competency*).
- Collections relating to animals used in proxy for human participants should be justifiable relative to the potential benefit to humans, having considered use of alternative methods, and adherence to ethical practices and regulations (see *C4. ELSI for Animal Specimens and Data*).
- Policies, procedures, and protocols for the life cycle of specimens and data should be reviewed by an ethics review committee where applicable (see *C1.3. Ethical Review*).

- Freely-given consent (*e.g.*, Prior Informed Consent (PIC) or informed consent) might be required before the collection of specimens and data (see *C2.2. Informed Consent Process* and *C4. ELSI for Animal Specimens and Data*).
- Participants/donors/providers whose specimens and associated data are collected and used for research should be provided with the right to refuse participation and withdraw from the process at any time (see *C2.2.5. Withdrawal of Informed Consent*).
- The collection, storage, and use of specimens and associated data should be conducted in a way that maintains the dignity, autonomy, welfare, privacy, and confidentiality of participants or legally authorized representatives (see *C1.4. Fairness and Equity in Repository Planning and Operations* and *C2.1. Managing Research Risks for Participants*).
- Measures should be taken to reduce risk to participants and ensure that any risks are weighed against the anticipated benefits of the expected findings (see *C2.1. Managing Research Risks for Participants* and *C4. ELSI for Animal Specimens and Data*).
- Repository governance should be designed to ensure the rights of potential participants and participants take precedence over the interests of society and other stakeholders (see *Sections A2.5. Elements of a Repository Governance Plan*, and *A3.2.3. Components of a Business Plan*).
- Processes should be in place to allow for return of specimens to participants or communities where feasible and appropriate or as required by any applicable indigenous code of ethics (see *C2.4. Posthumous Biobanking*).
- The interests and rights of participating communities should be protected in relation to benefit sharing, discrimination, stigmatization, and Indigenous Data Sovereignty (see *C1.4. Fairness and Equity in Repository Planning and Operations* and *C1.6. Research Integrity*).
- Other ethical principles, beyond those stated here, should be taken into consideration where applicable to reflect local perspectives and concerns.

***BEST PRACTICE:*** Repositories should carefully consider ELSI, assess associated risks and challenges, and incorporate these considerations throughout the design, management, and operation of the repository.

***BEST PRACTICE:*** Repositories undertaking new technologies and processes (*e.g.*, newly undertaking genetic analysis, considering collecting species/specimen types new to the repository) are urged to follow scientific and policy developments related to these new technologies and processes and to seek appropriate ELSI guidance, as needed.

## C1.2. Legal Implications

Repositories are responsible for understanding and addressing legal implications for their collections. The collection and use of specimens and associated data is regulated by differing regulations, laws, and policies that can apply at international, national, and local levels. Laws differ across the world and even where similarities may exist, the application of these laws may further vary by region or country. In addition, many countries do not have laws specific to repository activities, but other regulations may apply. Regulations in areas such as repository/biobank registration, research (*e.g.*, genetic and genomic), privacy and data sharing, ownership of specimens and/or data, health and safety, and shipping may be relevant to the repository.

Repositories that operate in multiple different regions (*e.g.*, multinational organizations, cross-border consortia) should be aware of the regulatory compliance laws of each region. For example, General Data Protection Regulation (GDPR)[16] pertains to European Union (EU) citizens' data, regardless of where the organization collecting the data is based. GDPR also applies to all data stored within the EU, even if the participants are not EU citizens.

As a further example, when handling microorganisms, animals, and plants (see *C3.*, *C4.*, *C5.* for ELSI for Microorganisms, Animals, and Plants), repositories should determine the applicability of the Nagoya Protocol relative to any regions where 1) specimens and data are collected, 2) the repository is located, and to where 3) specimens and data are distributed. Evidence of adherence to the Protocol (*e.g.*, Prior Informed Consent [PIC] and Mutually Agreed Terms [MAT]) is necessary to demonstrate appropriate regional application of the Protocol. A national focal point within the country of collection can be consulted for assistance. See the Access and Benefit-Sharing Clearing-House[17] for information on the countries where the Protocol has been ratified.

Repositories should therefore exercise caution in all operations, particularly for international exchange of specimens and associated data to ensure compliance with the regulations in the relevant locales.

Repositories may be challenged to meet regulations (*e.g.*, PIC/MAT under the Nagoya Protocol) or local guidelines (*e.g.*, Indigenous Data Protection) that require specimen data such as location of origin that is unavailable and must be retroactively obtained. The repository can consider developing a retroactive data acquisition plan that meets the needs of the stakeholders, such as indigenous and other underrepresented communities/populations, regulatory authorities, and experts, that clearly demonstrates accountability and integrity. Actions might include seeking expert guidance to ensure


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compliance, engaging stakeholders, conducting participatory research, and researching archives and publications to gather missing data. The plan should ensure stakeholder perspectives (particularly indigenous knowledge and cultural protocols) are respected throughout the process. Any new data should be documented and verified where possible according to the repository data management plan (see *Section I2.1. Data Management Plan*).

Determining ownership may be applicable for decision making about the specimens and data use or disposal. However, the determination of ownership, as well as the rights conferred by ownership, varies across jurisdictions. Additionally, regulations addressing questions of ownership may not exist for the jurisdiction of the repository. Further, regulations concerning the physical specimen may differ from regulatory requirements for the associated data. Repositories should take extra care to understand and continuously monitor the development of policies and guidance on specimen and/or data ownership that may impact repository practices. Specimen and data ownership and/or custodianship should be addressed in transfer agreements, such as material transfer agreements and data transfer agreements (see *Section K3. Transfer Agreements*).

#### C1.2.1. Compliance

The repository should have sufficient resources in place to oversee internal compliance. This includes the capability to determine, understand, and apply the relevant regulations, ratified treaties, and laws, as well as any relevant clinical or genetic research guidelines. Individual organizations may have local strategies that govern implementation of such applicable obligations. Repositories operating within a parent organization should leverage the organizational expertise, where available, and align with the organization's implementation of regulations and laws. Where repository compliance expertise is lacking, the repository should consult with external regulation experts or other compliance professionals or alternatively, use other methods such as recruiting the expertise required.

A culture of compliance starts with building an awareness within the repository of which regulations and legislation apply and promoting this culture throughout the repository. Policies and procedures can be used to effectively address all regulatory expectations and requirements deemed applicable. Compliance roles, responsibilities, and accountability should be clearly documented. Compliance expectations should be communicated in all aspects of repository activities, including managing personnel (*e.g.*, job descriptions, performance reviews) and conducting events such as recurring meetings, etc. Repository personnel training and competency assessment (see *Section E. Training and Competency*) is essential for fostering comprehensive understanding of and compliance to the relevant laws, regulations, and internal policies governing operations.

Regulations, legislation, and treaties can evolve with time. A repository should monitor for changes to existing relevant regulations and learn of new emerging regulations that impact their operations, including distribution. A repository should continuously review and update its policies and procedures to reflect changes. A comprehensive review of all the regulatory compliance areas should be conducted on a regular basis (see *Section D3.7. Auditing for Performance Review*). The repository should document the compliance process to ensure compliance is demonstrable.

Repositories should establish documented policies and procedures to ensure:

- Specimens and data entering the repository are acquired or collected in compliance with relevant regulations, and pertinent guidelines.
- Collections in the repository can legally be retained and used/transferred/distributed/disposed (see *Section K. Access, Distribution, Use, Transfer and Disposal*).
- When distributing specimens and data, relevant stakeholders such as end-users are made aware of their obligations to respect the terms and conditions governing use (see *Sections K2. Access, Distribution, and Use*, and *I2.1. Data Management Plan*).

***BEST PRACTICE:*** A repository should have sufficient resources and capability to understand the applicable regulations, and to oversee compliance.

***BEST PRACTICE:*** Interpretations of regulations and policies may vary; therefore, repositories should consult with relevant officials (*e.g.*, legal, ethics, and data privacy) within their organization for details on how regulations and policies apply to the repository operations and collections.

### C1.3. Ethical Review

An ethics review committee (institutional review board, research review board, or research ethics committee) is any group formally designated to review specimen collection plans and practices. Ethics review is well established for research involving humans or animals and can be applied to any type of repository engaged in activities with ethical and social implications. An

ethics review committee generally has the authority to review and approve such collections and to conduct periodic reviews to ensure the collection adheres to current ethical guidelines. In some countries, a national ethics body, a central ethical committee, or a biobank ethics committee may have the authority to approve the establishment and functioning of repositories of human specimens and data with the purpose of supporting health research.

During an ethics review, the processes and procedures for collection, processing, storage, distribution, and use of specimens and data for research are evaluated to ensure that these procedures are appropriate to protect donors/participants. This includes review of policies and protocols for obtaining informed consent, protecting the participant's privacy and the confidentiality of their data, and return of research results, where relevant. The repository approaches for compliance with data sharing mandates are also reviewed. The ethics review may include repository governance and oversight mechanisms for ensuring that use of specimens and data are for research that is scientifically and ethically sound (see *Section A2. Repository Governance*).

Where ethical review is a prerequisite, approval from an authorized body responsible for ethical review should be in place and documented prior to initiation of the collection. In accordance with the relevant ethics committee process, the repository should prepare documentation relating to the collection (*e.g.*, a research protocol, participant information, consent forms, procedures, etc.) to be submitted for review, where applicable. All correspondence with the ethics review committee, including any requests for alterations or further information, approvals or otherwise, and subsequent revisions should be stored and retained securely according to local regulatory frameworks and policies. Details such as specimen control practices and inventory data may additionally need to be submitted to appropriate parent organizational research standards and/or safety committees for review.

***BEST PRACTICE:*** Procedures and policies for governing and operating a repository should be reviewed by the appropriate responsible party to ensure all relevant ethical, legal, and social implications are considered and appropriate mechanisms are in place to ensure compliance.

***BEST PRACTICE:*** Repositories should require that the end-user's protocol for the use of specimens and data has been approved by an ethics review committee where relevant before granting access to repository specimens and data (see *Section K2. Access, Distribution, and Use*).

## C1.4. Fairness and Equity in Repository Planning and Operations

### C1.4.1. Benefit Sharing

#### C1.4.1.1 Overview of Benefit Sharing

Benefit sharing is giving some of the advantages or gains (including knowledge) that result from the use of repository collections to the communities or individuals who provided the specimens and data. This is particularly important if members of these communities do not have access to the products of the research, *e.g.*, new therapeutic options or diagnostic tests.

The concept and ELSI of benefit sharing were developed in the context of biodiversity research on non-human specimens and data[10]; however, the principles can be applied to repositories engaged in any purpose. Benefit sharing strives for fair and equitable sharing of benefits arising from the use of specimens and data with the participating communities, in line with national legislative or policy measures. Benefits can include:

- Sharing outputs (results, products, associating learnings) of research and development.
- Enabling collaboration in research or in development programs.
- Building education and training resources.
- Providing access to technologies on fair terms.
- Increasing social recognition.
- Funding (*e.g.*, grants) for salaries, research, or other purposes.
- Upfront investment or milestone payments in the project funding structure, to minimize barriers to entry and maximize inclusion and opportunity for Low/Middle Income Countries (LMIC) participation.
- Payments of royalties or license fees in the case of commercialization.
- Equitable sharing of intellectual property rights where applicable.
- Discounted costs for services.

Where relevant, benefit sharing may also be used to improve conservation and to support biodiversity.


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#### C1.4.1.2 Challenges to Benefit Sharing

The use of specimens and data by commercial entities is critical to scientific research and discovery, but raises a number of ethical, legal, and social issues. There may be real or perceived conflicts of interest between commercial and individual participant rights. Participants and communities may object to commercial use of specimens and data for cultural reasons that cannot be overcome through benefit sharing.

The challenges of benefit sharing may be more complicated when carried out between High-Income Countries (HIC) and Low/low-Middle Income Countries (LMIC) or among academic, for-profit, and government entities. Some communities, such as indigenous populations and other underrepresented communities, patients with specific diseases, etc., are sensitive to such collaborations, due to fears including misuse of specimens and data (*e.g.*, resulting in stigmatization or exploitation), and a lack of understanding of the social or cultural norms.

Sharing monetary benefits with human participants from discoveries made possible from using their specimens and/or data may be impractical or even inappropriate for a number of reasons. While specimens and data are a necessary part of research and development, the research process requires considerable resources and involvement by many entities. Typically, hundreds or thousands of individual specimens and/or data points contribute to research results, and it is extremely rare for an outcome to be attributable to an individual contribution. In addition, assigning value to an individual contribution raises ethical debate regarding the fair and equitable measurement of value.

#### C1.4.1.3 Strategies to Support Benefit Sharing

For benefits to be realized, equitable, and fair, repositories should consider the principles of benefit sharing when establishing governance policies (see *Section A2. Repository Governance*). The policies for benefit sharing should take into consideration the applicable laws, regulations, and viable implementation methods. In addition, the repository should consider the potential challenges and incorporate the views of all stakeholders, including participating communities and end-users (see *Section A5.2. Communication Strategy and Plan*). Benefit sharing should be explicitly contained in PIC/informed consent process, and in MATs/memorandums of understanding, or material transfer agreements (see *Section K3. Transfer Agreements* for formalizing stakeholder agreements).

If the repository contributes to or produces research output, the following strategies to support sharing potential benefits can be considered:

- Open science: an approach by which knowledge is made accessible throughout scientific research[18]. The core values of open science include collaboration, academic freedom, engagement, research integrity, collective benefit, equity and fairness, diversity, transparency, and inclusiveness. It should, however, be noted that open science may disproportionately benefit those with access to greater analytic resources[19].
- Open access publishing model: enables broader access to the results of research by eliminating barriers including limitations of copyright and reuse, and costs such as subscription and licensing fees. However, publishing fees may limit the ability of some repositories (*e.g.*, in LMIC) to leverage this model.
- Repositories (particularly those supported by public funds) make their resources, learning, results, and/or technologies publicly available (*e.g.*, publications of lay language summaries for general public consumption) and accessible with due consideration to ethical and legal obligations.

***BEST PRACTICE:*** Repositories should follow applicable national, regional, local, and international regulations and guidelines related to access and benefit sharing when planning collections.

***BEST PRACTICE:*** The governance policies should address the principles of benefit sharing within the remit of the repository operations.

***BEST PRACTICE:*** The repository should consider the challenges to benefit sharing and adopt strategies that support the repository policies on benefit sharing.

***BEST PRACTICE:*** Repositories that import specimens and data from other countries should ensure that fair and equitable benefits are made available to the communities from whom the specimens and or data originated.

### C1.4.2. Community Engagement, Inclusion, Diverse Participation

Engagement of participants and communities demonstrates respect for persons, supports transparency in repository activities, can provide important input on research participant perspectives and community values, and builds participant trust in the repository. Engagement of participants and communities can occur at many points throughout the repository lifespan, such as:

- Collaborative design of repository/collection, through surveys, focus groups, etc. (see *Sections A3. Repository and Business Planning* and *A5. Communication and Repository Promotion*).
- Informed consent process (see *C2.2. Informed Consent Process* and *C2.4. Posthumous Biobanking*).
- Governance and oversight, *e.g.*, participation in specimen use or other governance committees, ethics review committees, community advisory boards, etc. (see *Section A2. Repository Governance*).

The principle of justice holds that particular individuals, groups, or communities should not bear an unfair share of the burdens of participating in biobanking, nor should they be unfairly excluded from the potential benefits of participation. Repositories should consider diverse participation so that individuals and groups are not inappropriately excluded on the basis of attributes such as culture, language, gender, race, ethnicity, age, disability, or access to digital technology. Diverse participation in repositories helps to ensure that the research findings are as widely applicable as possible to all populations.

Repositories should consider the following aspects to respect potential participant communities and enable equitable participation:

- Language - the informed consent process and related documentation is in a language that can be understood by the participant; is sensitive to cultural, religious, and other issues; and any queries can be answered comprehensively and clearly by an appropriately qualified person.
- Gender - people should not be inappropriately excluded from research solely on the basis of their gender identity, and interactions with participants should be sensitive to issues of gender identity.
- Race/culture/ethnicity - efforts should be made to understand relevant cultural, ethnic, and religious codes of practice which may impact participation or the donation, storage, or distribution of specimens and data. Collaboration with the community, including religious and other leaders, can help promote dialog, mutual understanding, and the development of shared solutions to complex challenges. Some communities attach personal and cultural identity to specimens. In addition, some ethnic, religious, and indigenous groups may have beliefs about specific forms of research that are objectionable to them, *e.g.*, studies of ancestry, or have requirements regarding the disposition of unused specimens. Relevant policies may be available at national or other levels[20,21]. Discussions may cover a broad perspective and include the design of the research, the consent process, recruitment of prospective participants, appropriate uses of specimens and data, and dissemination of individual and collective research findings.
- Disability - People living with disabilities may require additional assistance to provide consent for biorepository storage. In some cases, these disabilities may require modification of written consent processes (for visually impaired persons), sign language interpretation (for hearing impaired persons), or assistance to individuals to access sites (for persons with mobility impairment). In the case where a person is considered incapable of providing consent because of mental impairment, a substitute decision maker may be required but, in these cases, wherever possible, assent should be obtained (see *C1.4.3 Vulnerable Participants*).
- Age - Elderly people and children (see *C2.3. Pediatric Assent Process*) should not be inappropriately excluded from research solely on the basis of their age.
- Geography - Efforts should be made to include potential participants living in remote, secluded, or sequestered areas, as appropriate, *e.g.*, indigenous populations in nation states, rural areas where transportation and access to health services are limited[21].

***BEST PRACTICE:*** When the repository focuses on the collection of specimens and data from a particular group or community, the repository should use appropriate engagement strategies to ensure that the community's perspectives, customs, and values are considered in the design, conduct, and/or oversight of the repository.

***BEST PRACTICE:*** If participant selection is within the repository's responsibility, the repository should design the participant recruitment plan and selection criteria to eliminate bias and monitor enrollment to ensure no individuals or groups are unnecessarily, inappropriately, or unjustly excluded from participation. Additionally, inclusion, diversity, and equity should be considered in all aspects of repository operations, data sharing/use, and specimen research.

### C1.4.3. Vulnerable Participants

A vulnerable participant is an individual or group who may require additional consideration or protection in the context of research, due to a potential for inequitable treatment, exclusion, coercion, or increased risk of individual or group harms. Vulnerability may occur as a consequence of the nature of the research and/or circumstances of the individual or group and may be either temporary or permanent.


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Participants may be vulnerable due to medical conditions, the stress of impending medical procedures, or heavy sedation. Vulnerable participants may also include those with dementia or syndromes of impaired consciousness, *e.g.*, coma, brain death, locked-in syndrome, and persistent vegetative state. Related ethical guidelines have been published by the British Medical Association[22] and the American Medical Association Council on Ethical and Judicial Affairs[23].

Other categories of vulnerable groups include: individuals in hierarchical (subordinate) relationships or those who historically had little recourse to protect their interests and needs; institutionalized persons, *e.g.*, those in mental institutions and prisons; women; some ethnic and racial minorities; those living with stigmatized, incurable diseases, or disabilities; those receiving welfare or social benefits; the poor and unemployed; and homeless persons[3,21].

In addition, potential groups could become vulnerable through the sharing of research results pertaining to their participation (*e.g.*, concerns about insurability following new disease-gene association discoveries, or about risk for victimization by law enforcement). See *C2.6. Return of Research Results* for additional information on this practice.

Repositories should be aware that a state of vulnerability may be temporary, *e.g.*, a child reaches adulthood, a medical condition may resolve, or declaration of a state of emergency due to natural disaster. The repository should monitor its collections and take appropriate actions when a participant's status changes, *e.g.*, obtaining or updating consent or authorization.

Repositories should be well-versed with the ethical, legal, and social implications when working with specimens from vulnerable participants. Recruitment of participants to any type of research should be equitable. A repository should be aware of any additional needs and equity of treatment for vulnerable or underrepresented groups among prospective participants[15].

Extra care and attention should be given to the consent process when participants have limitations in their capacity to consent. In cases of mentally incompetent participants, a relative or legally authorized representative may sign the consent form on the participant's behalf. In some regions, the participant must be informed regardless of their age, medical, or mental condition. See *C2.2. Informed Consent Process* for additional guidance on this practice.

***BEST PRACTICE:*** A repository should identify and address any additional needs and equity of treatment for vulnerable or underrepresented groups among prospective participants.

***BEST PRACTICE:*** Special measures should be taken when obtaining consent for use of specimens and data from participants who have limitations in their capacity to consent.

### C1.4.4. Impartiality

Repository personnel should act impartially, using established policies and procedures to make consistent decisions based on objective criteria and intentionally eliminating bias, prejudice, or benefitting one over another for improper reasons. Any undue pressure exerted by other parties (from within and external to the repository) or conflict of interest regarding the access and sharing of specimens and data should be declared (see *Section K2. Access, Distribution and Use*).

Bias and prejudice can be unintentionally introduced into any repository process that requires persons to make choices based on variable, subjective, incomplete, interpreted, or complex information. Primary examples of such processes are participant selection, obtaining consent, and application of access and use policies. Participant selection can be biased due to insensitivities in the design (*e.g.*, excluding persons without access to a computer by requiring digital consent). Prejudice may influence whether prospective participants are approached for consent or prevent successful consent. Reviewer bias toward specific research objectives, an applicant's credentials, or personal political agendas may affect approval or prioritization of requests for repository resources.

The concept of impartiality includes addressing conflicts of interest (COI), which is a real, potential, or perceived situation in which an individual's interests could result in personal, professional, or organizational benefit. A COI may arise when activities or situations place an individual or institution in a real, potential, or perceived conflict between the duties or responsibilities related to repository activities, and personal, institutional, or other interests. These interests include, but are not limited to, professional pressures; academic ambition; and business, commercial, or financial interests pertaining to the institution and/or the individual, their family members, friends, or their former, current, or prospective professional associates.

Repositories should work together with organizational leadership to develop and implement policies and procedures to identify, eliminate, minimize, or otherwise manage bias, prejudice, and conflicts of interest that may

affect the repository operations. Any real, potential, or perceived partiality of which the repository is aware should be disclosed to the oversight authority identified by the policy to determine the appropriate steps to manage it.

The repository should train personnel on its policies and procedures designed to achieve impartiality. All repository personnel should be trained to recognize and avoid conditions that may lead to conflicts of interest. Personnel in positions that require interaction with stakeholders, including participants, the community, or end-users, should receive introspective training focused on uncovering and eliminating personal biases and prejudices.

***BEST PRACTICE:*** The repository should develop and implement a policy and procedures to identify, eliminate, minimize, or otherwise manage bias, prejudice, improper preference, and conflicts of interest that may prevent the repository from acting impartially.

## C1.5. Environmental Impact and Biobanking

While not traditionally considered part of ELSI, environmental ethics acknowledges the connections between repository activities, research, and the environment and ecological impacts. Recognizing the need to minimize harm and promote sustainability and environmental justice, repositories should strive for responsible and efficient use of resources. A repository should consider facility and equipment management strategies to minimize its use of land, energy, chemicals (*e.g.*, industrial cleaning agents) and liquid nitrogen in its operation (see *Sections F4.11. Environmental Safety and Sustainability*, *G1. General Introduction to Facilities*, and *H1. General Introduction to Storage and Processing Equipment*). Liquid-nitrogen-cooled storage units, ambient-temperature storage formats, retaining specimen data only, and routine selective disposal are opportunities for repositories to demonstrate environmental stewardship.

Repositories can take further proactive measures to reduce environmental impact by sharing specimens and data to reduce the need for additional collections, where practicable and permissible, and taking care to collect responsibly when necessary[24]. This might additionally help to meet the expectations of participants/donors rather than allow specimens and data to go unused or underused. International and national biodiversity initiatives encourage sharing and establish rights and responsibilities for specimen collection, applying the concepts of environmental stewardship and benefit sharing to additional domains and extending geographical reach[14,25]. These collaborative efforts serve to not only improve research capability, but reduce further collections of endangered and vulnerable species. Additional information regarding environmental protection and preservation is provided in *C3. ELSI for Microbial Specimens and Data*, *C4. ELSI for Animal Specimens and Data*, and *C5. ELSI for Plant Specimens and Data*.

Respect for spiritual concerns and compliance with land rights for indigenous natives are key ethical, legal, and social issues in the biodiversity space. For these often-vulnerable groups (see *C1.4.3. Vulnerable Participants*), their spiritual connection with the land is an important part of their culture, with their identity and wellbeing strongly linked to the land's health, and their ability to access its resources for cultural practices and traditions (*e.g.*, fishing, hunting). Where environmental repositories are being developed within such cultural lands, local environmental protection agencies and related legislation should be consulted in the early stages of planning to ensure associated perspectives and sensitivities are considered.

Biobanking Involving Environmental Research

Repositories are finding new opportunities in areas of research that combine specimens and data from multiple biological (including human and/or other species) and non-biological sources. These opportunities may present challenges (in particular for consent, impartiality, and access and benefit sharing [ABS]) that require new and modified ELSI practices as legislation, regulations, and guidelines evolve. Several emerging considerations include:

- The One Health Initiative represents a worldwide strategy for interdisciplinary collaborations in all aspects of health for humans, animals, and the environment[26]. Global research is expanding from single gene-focus to omic factors and systems biology within and across complex disease relationships[27]. This shift will give rise to ELSI regarding the integrated use of human, animal, and other environmental materials, with the topic of consent requiring primary attention. While human biobanking is currently largely focused on improving public health, participants in One Health biobanking may need to provide informed consent for their specimens and data to be used for integrated research for public, animal, and environmental health.
- Environmental biobanking is used by some governments to target biodiversity and publicize their commitment to the Convention on Biological Diversity[10] and environmental areas of the Sustainable Development Goals (SDGs) of the United Nations[28]. These efforts may introduce conflicts of interest as different factions compete for resources and seek to influence repository policies. Repositories should revert to their established impartiality policies and procedures in such instances (see *C1.4.4. Impartiality*).
- Ecosystem mapping and biomonitoring using environmental sampling is a developing area in international biobanking.



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Specimens are stored in Environmental Specimen Banks (ESBs) to enable the analysis of DNA, RNA (*i.e.*, environmental DNA [eDNA] or RNA [eRNA]) and proteins from both tissue and non-biological substrates such as soil and water[29-31]. ELSI challenges relate to management and stewardship of genomic samples and their derivatives, including appropriate access and benefit sharing[32].

Repositories involved in such initiatives should periodically review their established policies and procedures to ensure that the emerging ELSI guidelines and/or regulations are evaluated for compliance (see *C1.2.1. Compliance*).

### C1.6. Research Integrity

Research integrity principles include honesty, accountability, respect for individuals and community, professional courtesy, and fairness, as well as good stewardship of the research[20, 33].

Repositories have a role in ensuring research integrity through the use of verified methods, known standards, and the reporting of results without bias. Repositories should be impartial (see *C1.4.4. Impartiality*) when reviewing access and use requests (see *Section K2.2. Review of Access and Use Requests*) and when negotiating or administering contractual agreements (see *Section K3. Transfer Agreements*). Further, the repository should establish practices that honor any agreements, regulations, or policies regarding data sovereignty for participant communities.

Repositories should be transparent in their processes. Repository practices enabled by strong quality management are validated and verified with documented policies and standard operating procedures (SOPs) (see *Section D3. Quality Planning*) supporting transparency. Repositories must maintain confidentiality of participant/donor data as well as proprietary information of the end-user (*e.g.*, research outcomes). This practice should be in conjunction with applying FAIR (Findable, Accessible, Interoperable, and Reusable) Principles for data (see *Section I2.2. Data Management System*), where appropriate. Transparency also includes appropriately acknowledging attributable contributions to the outcomes of repository activities; for example, referencing precedent research, recognizing use of indigenous knowledge, and publicizing funding sources and allocations[19].

Research reproducibility depends on the correct association of accurate data with specimens (see *Section I3. Inventory Management System*). Some repositories contribute to research integrity by maintaining and providing voucher specimens for plant, animal, and microbial species, which serve as known standards against which research material can be verified (see *C5.3. Voucher Specimens*).

The emergence of sophisticated artificial intelligence (AI) engines, capable of producing credible SOPs and research papers, presents both opportunities to advance research and ethical challenges to research integrity. For example, AI can improve accuracy and reliability of research, but machine learning can develop bias in the same manner that people adopt bias through the influences of the input[34]. Beyond research integrity, the ELSI of AI impact multiple areas, including benefit sharing, impartiality, and managing research risks[35]. Repositories should assess the potential uses and ethical implications of AI and monitor for new and updated regulations (*e.g.*, human rights, data protection) and guidelines[36,37] as adoption of this technology expands.

Repositories have a responsibility to ensure that personnel act with integrity. Training is an effective tool that raises awareness of the potential situations and influences that may lead to bias and inaccuracy. The repository training and competency program should inform personnel of the policies and procedures in place that are designed to encourage and support ethical behavior or help avoid unethical decisions or actions (see *Section E. Training and Competency*).

## C2. ELSI FOR HUMAN SPECIMENS AND DATA

The ethical conduct of research involving human specimens and data from repositories is crucial for participant protection, as well as establishing and maintaining the trust of participants, the public, and other stakeholders. Furthermore, it is essential for participation in research, advancements in science and medicine, and repository sustainability.

### C2.1. Managing Research Risks for Participants

While there is generally minimal direct benefit to participants whose specimens and data are collected, stored, and used for research, the availability of specimens and data from repositories contribute greatly to scientific and medical advancements. These advancements depend upon the altruism of individuals to participate in research for the purpose of benefiting others.

While much of repository supported research is considered to be of minimal risk for participants, such risks should be assessed and managed. Risks may include physical hazards, *e.g.*, incurred due to a blood draw, or taking a biopsy in addition to that required for clinical necessity. Risks may also include loss of privacy and confidentiality, and potential harms resulting from disclosure of information, such as embarrassment, stigmatization, loss of insurance, or employment.

Respecting individual privacy and confidentiality with respect to specimens and data should be considered in a context that includes risks and benefits to family members, community, and identified populations. Group risks should be carefully considered. For example, stigma or dignitary harms to groups may occur even when specimens and data are considered de-identified through coding or anonymization (see *C2.1.1. Privacy and Confidentiality Risk*).

Care should be taken to identify potential sources of risks to participants, to minimize these and ensure that risks do not outweigh the benefits. This includes minimizing physical 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. Participants need to be informed of any potential risks and the measures in place to mitigate these risks during the informed consent process in order for them to make an informed decision (see *C2.2.1. Obtaining Consent*).

For more information on risk management practices for repositories, see *Section B1. Risk Management*.

### C2.1.1. Privacy and Confidentiality Risk

The repository should have safeguards, such as policies, in place to protect the privacy of participants and the confidentiality of their data, and define the response consistent with applicable regulations and laws in case of privacy breach. In addition, the repository should train personnel to maintain privacy of participants, protect their data, and monitor for compliance. These safeguards include the following secure data storage strategies (see *Section I2.3. Data Security and Privacy* for further information):

- Physical security such as locking filing cabinets and placing computers in restricted access areas.
- Administrative procedures such as limiting access to information on participants or other sensitive data through role-based security (see *Section I2.3.1. Data Security*).
- Technical protection such as computer passwords, firewalls, anti-virus software, encryption, and other measures that protect data from unauthorized access, loss, or modification.
- Timely deletion of data in accordance with record retention policies (see *Section D3.2.2. Storage and Retention of Documented Information*) and jurisdictional legislation.
- Coding data that could otherwise be used to identify an individual, or reveal health or other sensitive information of an individual.

The repository should follow well-documented procedures to protect the privacy and confidentiality of the participants from whom the specimens and/or data are obtained. Coding and encryption are often used to protect the privacy of the participants and the confidentiality of their data. Different approaches for handling specimens and personal sensitive data for privacy are provided below:

- **Identified** human specimens and associated data are identified through use of a personal identifier (*e.g.*, name, national census identifier, or medical record number). Identification is maintained when repositories are responsible for data collection from the clinical record such as diagnosis, treatment, and outcome. It is the duty of such repositories to treat personal information in a confidential manner and collect only the minimal identifiable information necessary.
- **Coded** human specimens and data (also referred to as pseudonymization) have direct identifiers removed and replaced with a code. Repositories may be responsible for coding specimens and data and maintaining that link. This task introduces the risk of creating identity errors.
- **Anonymized** specimens and data are irrevocably stripped of direct identifiers. This method is not usually associated with repositories where ongoing collection of participant data contributes value to the specimens.
- **Anonymous** specimens and data are collected without direct identifiers. This method is the most protective of participant confidentiality[21].

Identifiable and coded specimens and data are at risk of privacy breaches of participant data, which can potentially harm participants or groups to which they belong. Any risk of re-identification and associated harms to participants should be discussed during the informed consent process.

### C2.1.2. Physical Risk

Physical risks in the collection of specimens may result from the invasiveness of the collection procedure and amount of specimen collected. Examples of physical risks range in severity from minimal risk of urine collection,


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bruising and fainting with blood collection, discomfort, and bleeding upon bone marrow aspirate, to internal bleeding resulting from deep tissue biopsy and infection resulting from any invasive procedure.

There are several reasons to minimize the volume or size of specimens to be collected. Restrictions may be imposed by regulations, cultural agreements, or oversight committees. Practical limits may apply when collecting specimens during a clinical procedure, but this practice may be preferred to minimize incremental risk of the procedure. Ancillary collection during more invasive procedures may not be ethically approved based on risk to the participant.

A potential risk from the secondary use of clinical specimens emerges if such use affects the availability or usefulness of specimens required for clinical care. Some clinical specimens (*e.g.*, ascites) may be ideal for repository collection if they are collected for clinical care and would otherwise be disposed of without the need for diagnostic review. Other clinical specimens (*e.g.*, fresh surgical tissue sampling) carry an additional risk of interfering with clinical results and diagnosis (and subsequent healthcare) when collected before diagnostic results are complete. There is potential for exhaustion of stored clinical specimens that may be needed for future clinical care. There is also potential harm from treating participants based on individual research results that have not been analytically and clinically validated. Collections presenting risk to clinical care should be performed under the supervision of a pathologist to mitigate the risks.

### C2.1.3. Psychosocial Risk

Repository personnel who interact with participants in stressful situations (*e.g.*, healthcare settings, death) must be trained and supported to handle psychosocial risks. Psychosocial risks that may arise during the consent process include adding stress or influencing the participant's decisions regarding their situation. In addition, individuals may be concerned about the potential for dignitary harm or social stigmatization due to inadvertent release of participant information or research results. Psychosocial concerns also surround sensitive tissue types and socially controversial topics. The repository training program should address the psychosocial risks specific to the mission and collections.

Minority, ethnic, religious, and social groups or communities may be at risk of harm due to the release of aggregate research findings 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. Consideration should be given to these issues during the planning phase prior to collection to ensure that cultural, religious, and other perspectives of the research population and community are respected.

***BEST PRACTICE:*** Every effort should be made to protect participants' privacy and confidentiality of sensitive data associated with human specimens. Measures that are taken to protect participant privacy and confidentiality should be shared during the informed consent process (see *C2.2.1. Obtaining Consent*).

***BEST PRACTICE:*** To protect participant privacy and confidentiality in the use of health data associated with human specimens, repositories should ensure that participant identifiers are removed either prior to receipt (by the source) or prior to release to approved end-users. Any exception to this should be in line with applicable ethical and legal requirements, be clearly justified and documented.

***BEST PRACTICE:*** The repository should ensure that collection of specimens and/or data for research does not adversely affect patient care.

***BEST PRACTICE:*** The repository training program should provide personnel the capability to manage and minimize the privacy, physical, and psychosocial risks relevant to its operations.

## C2.2. Informed Consent Process

Informed consent is generally recognized as an ethical prerequisite for research collections involving human participation; however, exceptions and variations exist across geographical regions or countries. For example, community-based decision-making, exemptions, or opt-out approaches can affect the process. Additionally, due to the nature of research supported by repositories (often future unspecified research), the informed consent process may differ from that used for many other types of medical research, such as preclinical and clinical models.

Repository planning (see *Section A3.1 Repository Planning*) should include consideration of the repository's role in the consent process and how the repository will meet applicable laws and regulations. The repository should determine the appropriate consent model or models, if applicable to the repository's role in the process.

### C2.2.1. Obtaining Consent

Informed consent for the collection, retention, and use of specimens and data is a process that offers participants/communities sufficient information to enable an informed choice to donate specimens and data and to agree, where applicable and desired, to future research use. Consent should only be obtained under circumstances that provide the prospective participant (or the participant's representative, such as community leaders or a parent) sufficient information and opportunity to consider whether or not to donate. The information that is provided should be understandable to the participant or their representative, according to the level of knowledge and education of prospective participants. The process should minimize the possibility of coercion or undue influence. A separate consent may be required for research or use other than those originally outlined.

The type of consent must be in accordance with applicable national, federal, regional, and 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 uses of specimens and data are consistent with the original consent. This objective may be achieved through review by an ethics review committee or other mechanisms consistent with applicable regulations, laws, ethical approval, and repository guidelines.

Informed consent is a two-way communication process between the collector and the prospective participant/representative that can result in a documented agreement between the two parties. Such a process should be led by trained, competent personnel who can communicate, interact, and respond to the questions and points raised by prospective participants. Sufficient information should be provided in any consent model to allow competent participants or their representatives to make a voluntary informed decision. The repository should include information about the consent in its data management plan (see *Section I2.1. Data Management Plan*). Through the communication process, competent personnel should observe the prospective participant's capacity to understand the information and consent, and consider if the consent is ethically viable. Consent should be obtained preferentially from the participant who will donate specimens and data, or from:

- An authorized third party on behalf of a participant who lacks decision-making capacity; the authorized party is responsible for taking into account any research directives of participant.
- The deceased participant through a donation decision made prior to death.

In the context of research involving a community (see *C1.1. Ethical Principles and Recommendations*), informed community consent might be an additional requisite; however, obtaining individual informed consent remains important, especially where personal or sensitive information about specific individuals within the community is sought.

Collection should begin only after the participants, or their authorized third parties, have provided their explicit consent. Explicit consent is the documented written or verbal agreement by an individual to contribute specimens and/or associated data for use in research and may include a broad consent or other type of consent (see *C2.2.2 Types of Consent*).

The repository should plan for storage of signed consent forms, if retained by the repository, addressing storage format (*e.g.*, paper, electronic) and storage backup (see *Section I2.1. Data Management Plan*). Exceptions may occur under limited conditions, such as when archived residual specimens and data are used for future research, or when the appropriate ethics review committee or relevant authority deems that explicit consent is not required. The use of exceptions (*e.g.*, consent waiver or exemption) is generally dictated by jurisdictional regulatory framework. Repositories seeking exceptions should consult with the relevant authority to ensure the granting and application of any such exception is in line with governing regulations and guidelines.

Prospective participants' autonomy and freedom of choice should be emphasized, including that the choice of non-participation does not affect their rights to receive treatment and will not lead to any discrimination against them. Requiring prospective participants to bear expenses to participate can result in exclusion or less diverse participation (see *C1.4.2. Community Engagement, Inclusion, and Diverse Participation*)[3]. Where compensation for participation is provided to individual participants and/or communities, every effort should be made to avoid undue influence or coercion.

While requirements for informed consent may vary according to national law and local guidelines and policies, the consent documentation should at a minimum describe the following: privacy, confidentiality and data protection mechanisms, specimen and data retention time and storage conditions, and whether or not research results are expected to be returned (see *C2.6. Return of Research Results*). Additional information provided during the informed consent process can include[6,8,38]:

- Definitions for key terms, *e.g.*, biobank/repository/biorepository.



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- The purpose or mission of the repository or collection.
- Information regarding repository governance.
- Description of the intended use of participant's specimens and data, including any commercial use, genetic/genomic research (including potential genomic sequencing). If a specific consent for genetic/genomic research is required, this should be mentioned during the communication process.
- The right to withdraw consent and how this is operationalized (see *C2.2.5. Withdrawal of Informed Consent*). A clear statement if the option of withdrawal of consent is not available and the reason (*e.g.*, due to irreversible anonymization).
- Access and sharing conditions of specimens and data, including sharing with local or international end-users for the intended use.
- Types and amount of specimens and data to be collected.
- The manner in which specimens and data will be collected, including the safety and invasiveness of the acquisition procedures.
- Participants' rights, benefits, any compensation for risks and burdens associated with collection and use of specimens and data (see *C2.1. Managing Research Risks for Participants*). This is particularly important if research involves vulnerable, indigenous, or other underrepresented communities/populations.
- Possibility of re-contact, including whether individual results or incidental findings will be returned or not, and the procedure for these actions (see *C2.6. Return of Research Results*).
- Intellectual property rights, commercialization, and benefit sharing.
- Any relevant sensitive belief, or local or cultural issues that might impact participation.
- Explanation of what happens to the participant's specimens and data upon death or other change in capacity to consent.

With a focus on transparency, an information sheet in the form of questions and responses addressing these points can be used as a supplement to be provided to potential participants in advance of the discussion on informed consent. Audio-visual aids can additionally be used as an engagement method.

If specimens and data are stored beyond the anticipated retention period, or if regulations governing retention and storage change, the informed consent should be reviewed and updated where necessary for fitness for purpose and compliance. The revised consent documentation and process should be reviewed for approval by the ethics review comment or relevant authority. The changes may require the repository to take further action such as obtaining re-consent from the participants.

Repositories commonly use opt-in consent approaches (as described above), where potential participants take a positive or affirmative explicit action to agree to participate. However, it might be possible in certain circumstances and with due ELSI consideration to use a different approach such as a waiver of consent or opt-out of consent. In these approaches, there is a presumption of consent by default; individuals are automatically included unless they take action to indicate their preference to the contrary. Repositories should always consult applicable regulations and the relevant ethical framework to assess waivers or opt-out approaches. The following points are relevant:

- Circumstances: A waiver of consent or opt-out of consent approach might be necessary during emergencies, for use of residual anonymized clinical specimens of high-value, or if the research cannot be carried out without the waiver.
- Justification: Use of waiver/opt-out approaches should be carefully justified relative to the potential benefit, having considered all alternative options. The involvement of vulnerable groups, tissue types requiring sensitivity, or use of controversial techniques needs to be addressed during justification.
- Authorization: Where deemed an appropriate or only viable option, waivers, and opt-out approaches should be carefully assessed (*e.g.*, impact assessment) before submission for review and approval by an ethics review committee or appointed authority.

***BEST PRACTICE:*** Sufficient information should be provided during the informed consent process to allow prospective participants or their representatives (such as community leaders or parents) to make a voluntary informed decision whether to participate. Prospective participants and/or their representatives should be encouraged to ask questions and be provided with sufficient time to make an informed decision.

***BEST PRACTICE:*** Every effort should be made by the repository to avoid undue influence or coercion of prospective participants and prospective participants representatives.

***BEST PRACTICE:*** The rights of prospective participants, including autonomy and freedom of choice, should be explained during the informed consent process.

***BEST PRACTICE:*** A repository should ensure that participant consent is sought prior to initiation of specimen and/or data collection, except in situations where an alternative legal basis (*e.g.*, waiver, opt-out, deferred consent) is applicable and has been specifically approved by an authorized ethics review committee or relevant authority as per the relevant laws, regulations, and ethical principle and frameworks.

***BEST PRACTICE:*** If the retention period or retention/storage requirements change for the specimens and/or data, the informed consent should be reviewed, and where necessary updated, and submitted for re-approval by the relevant authority, and any necessary follow up actions should be taken to ensure valid consent.

### C2.2.2. Types of Consent

The repository should carefully consider the model of informed consent that suits the purpose of the collection. Considerations include the scope of research activities of the repository and end-users, the applicable laws and regulations, the culture of the communities relative to participants, organizational policies, and the available information technology (IT) infrastructure within the repository and the participant community.

Several alternative models of informed consent exist for use by repositories, each having advantages and limitations as described below. A repository can use one or multiple consent model(s), and some consent models can be combined. Repositories should evaluate the complexities of the potential consent models in consideration of the scope of its mission, the longitudinal expectations of the collection, its budget for infrastructure and personnel to maintain (and potentially continuously update) the consent records, and the potential to bias the participation due to cultural or infrastructure implications.

The implementation of consent models and associated documents used by a repository should be reviewed and approved by the appropriate ethics review committee or relevant authority.

**Specific consent** details the exact nature and scope of the intended research and its potential benefits and risks. Repositories often collect and store specimens and data for unknown and non-specific future research, which challenges the practice of specific informed consent. If a specific consent model is used at the time of collection, a new consent could be required for research that falls outside the scope of the signed consent. Re-consent can be burdensome for both repository representatives and participants, which may limit the ability of the repository to fulfill its role in supporting research that falls outside of the scope described for the specific consent.

An example of an approach using multiple consent models is a clinical research trial for which residual specimens will be banked for future use. In this case, two consent types might be used: a specific consent for the trial, and a second broad consent for the banking of specimens and/or data.

The **broad consent** model supports the collection of specimens and data for future, unspecified use within a broad set of parameters. It allows flexibility in that additional consent from participants is generally not required. The consent document should contain information that bounds the potential future use, which can include details about the scope and goals of the repository and the governance policies with respect to consent for future use. To maintain accountability to the participants, the repository governance can include an oversight committee, *e.g.*, a specimen and data utilization committee, responsible for authorizing research per the consent.

Jurisdictional differences exist for broad consent definition and/or its application. Some regulations outline conditions and limitations for its use (*e.g.*, "Regulatory Broad Consent" US Common Rule[39]), while other jurisdictions and certain populations may not recognize broad consent as a valid consent model. Where used, regulatory conditions might include information specifications, to provide transparency and demonstrate respect, coupled with a robust governance system (including a competent ethics review) to oversee a well-designed process that is executed with integrity. Ongoing communication and engagement with participants are further recommended to mitigate risks of informational harm and violating ethical principles, such as autonomy[40].

A **tiered or multilayer consent** model empowers participants to give consent to specific types of research or uses; for example, research focused on a particular disease. This approach allows participants to select how specimens and data will be used through their responses to specific questions. This model gives participants greater control over the use of specimens and data by providing options and enabling engagement in a way that suits the participant. This approach can increase the complexity of the consent process, and so careful design to present information in a clear and accessible manner (*e.g.*, using support materials such as visual aids to help present the options) can help to avoid confusion and decision fatigue for participants. Implementing multilayered consent models can add additional administrative burden for repository personnel including for compliance. This model benefits from sufficient ongoing resources (*e.g.*, IT infrastructure, competent personnel, protocols,


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oversight during preparation of specimens and data) to track participant choices (which may change over time) and ensure the use of the specimen and data follows the participant's expressed desires.

The **dynamic consent** model uses technology to allow participants to manage their preferences over time and to choose between broad consent or to consent to one project or study at a time. The consent is presented in a digital platform, which enables participants to review their preferences and decisions. This model is flexible and allows participants a higher degree of autonomy than one-time consent models. In addition, it may facilitate better understanding of research through the use of audio-visual or interactive tools, which could also be used to engage more potential participants as a communication and promotion tool (see *Section A5. Communication and Repository Promotion*). The main limitations of this model are related to the need for the presence of a strong IT infrastructure and good internet connection for participants, which challenges the use of this model in limited-resource settings. Moreover, although this model can provide information to the participants about the research to be conducted, the potential for confusion, misinterpretation, or misperceptions could negatively affect decision making. Participants might also become less responsive over time, which could limit the use of their specimens and data. In addition, it may discourage participation of those who do not have access to or are uncomfortable using IT and potentially bias representation in the collection.

**Deferred consent,** also known as research without prior consent, may be used as permitted by an ethics review committee or relevant authority (*e.g.*, in emergency settings from incapacitated patients at the time of specimen/data collection)[41]. Deferred consent is generally used in time-sensitive situations and involves enrolling participants without obtaining their informed consent in advance. This model is of particular value during public emergencies or pandemics, where collection of specimens and data for future research is of utmost importance but conducting a formal informed consent process is not feasible. As soon as possible (*i.e.*, after the emergency/urgency has resolved), the options for informed consent or immediate withdrawal should be presented to the participant or their legal representative. The consent should be carried out according to the approved research protocol and applicable laws and regulations.

Regardless of which model(s) of consent are used (see *C2.4. Posthumous Biobanking* for information on consent/authorization related to posthumous biobanking), discussion and communication of the informed consent can be facilitated using either face-to-face or remote interactions. The latter can be done by mail or through internet-based (digital) tools. Digital approaches provide advantages such as interactive multimedia tools, convenient access for potential participants, and more time for decision making. However, the main limitation associated with this approach is lack of sufficient infrastructure, particularly in LMIC (see *C1.4. Fairness and Equity in Repository Planning and Operations*). This approach could also be associated with legal and/or technical barriers. Moreover, some participants could be more comfortable with direct face-to-face interaction or might be unwilling to use digital media. Even if the repository does not use digital options for consent communication, it can still establish a donor-accessible website to provide information on ongoing research projects to keep potential donors informed about its activities (see *Section A5.2. Communication Strategy and Plan*).

***BEST PRACTICE:*** Each repository should choose a model (or models) of informed consent according to criteria including: the scope of research activities of the repository, the applicable laws and regulations, the culture of the participant community, and the available infrastructure.

***BEST PRACTICE:*** The implementation of consent and associated documents used by a repository should have prior approval from the appropriate ethics review committee or relevant authority (see *C1.3. Ethical Review*).

***BEST PRACTICE:*** The repository should monitor the application of the approved consent process, to ensure that the general principles of informed consent are followed and should comply with reporting requirements.

### C2.2.3. Consent for Secondary Use

Secondary use refers to the use for research of existing material or information (often both) that were originally collected for a purpose other than the current research purpose. Examples of biological materials include specimens left over from diagnostic examination or a surgical procedure, or that were collected for an earlier project. Secondary data may come from health care records, registries, and other sources.

Reasons to consider secondary use include avoiding duplication of the primary collection and applying new processing or testing methods. To realize the full potential of personalized medicine, repositories are providing health data associated with participants to enable big data analyses of lifestyle choices, environmental exposures, clinical outcomes, specimen-derived multi-omic data, and other sources[42,43].

However, several challenges exist for secondary use in relation to informed consent, data/specimen identifiability, inequitable distribution of benefits, and using data across geopolitical borders. Many of these issues arise due to the differences in national and regional participant and data protection regulations, differing interpretations of regulations, and the evolving nature of regulations in these areas. Several global frameworks have been proposed to promote a harmonized approach to resolve these issues to advance science while protecting individual rights[44,45].

The repository should seek an ethics review of the proposed secondary use (see *C1.3. Ethical Review*), although depending upon the nature of the use and local policy, consent for the secondary use might be waived[21].

***BEST PRACTICE:*** Where secondary use is planned, repositories should consult their local ethics committees, organizational policies and data protection officials, and applicable regulations and legislation to determine the repository obligations regarding secondary use of specimens and associated data. The repository should establish and implement protocols for secondary use including the measures required to ensure requirements are met.

### C2.2.4. Declined Consent

The informed consent process should emphasize the voluntary nature of participation. Individuals have the right to decline participation and may refuse to provide specimens or data at any time. In the context of health care, clear information should be given to the individuals that their clinical care will not be negatively affected in any way by their decision to consent for further use of their specimens and associated data. For quality improvement and to gain insights into participant perspectives, repositories can track overall rates of consent and reasons given for declining. The repository should comply with any ethical or legal restraints that apply to tracking of refusals. By assessing reasons for declining, a repository can address specific concerns, and potentially update the consent documentation or process to improve enrollment rates. The repository should document and track that no specimens/data have been collected/acquired/stored when consent has been declined, and additionally where select purposes (such as genomics or commercial uses) were declined by the participant.

If specimens and/or data without corresponding consent are stored in the repository, a clear explanation should be documented justifying the legal basis for storage. Where no justification is available, the repository should inform the relevant stakeholders (such as repository governance, ethics committee or relevant authority, the participant community, and legal experts) to seek guidance on the best course of action and determine lawful and ethical actions that are respectful of the individual's rights. All actions taken should be documented and safeguards implemented to prevent a recurrence.

### C2.2.5. Withdrawal of Informed Consent

Participants or their representatives should have the right to withdraw consent and to have their identifiable unused specimens and data removed from the repository. At the time of consent, the repository should inform participants of their right to withdraw and the process for withdrawing consent. The logistics for how such a request is initiated and enacted should be specifically outlined in the informed consent document and should be straightforward and easily comprehensible. Additionally, the effect of withdrawing consent should be outlined, including disposal or return of specimens and non-retention of data. Any limitations on withdrawal should also be described. For example, it may not be possible to retrieve specimens and associated data once they are anonymized or distributed and used for research (see *C2.2.1. Obtaining Consent*).

The process for withdrawal of consent should be supported by the repository infrastructure. Communication channels for participants or their representatives to contact the repository, as provided in the consent documentation, should be maintained for the entire period the consent is valid. The repository's communications should include plans for keeping participants (and the relative communities where applicable) informed of changes that could impact their participation (see *Section A5.2. Communication Strategy and Plan*). Consent and withdrawal of consent records should be handled according to the repository records management system (see *Section D3.2. Documentation Management and Control*). Repository personnel should be trained to properly respond to withdrawal of consent (see *Section E. Training and Competency*). The repository inventory management system should enable withdrawal and disposal of specimens and data, along with recording the withdrawal of consent (see *Section I3. Inventory Management System*).

Where possible, the specimens and data should either be disposed of or returned to the participant, their representatives, or the participant community according to the process outlined in the consent.

Where the participant expresses a desire to continue participation while changing their original consent specifications, options for continued altered participation that a repository might support include:


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- No further contact by the repository for current or further research studies: Continued retention and use of previously obtained specimens and data is permitted, as well as access to data from health records (if included in the original consent approval).
- No further access to health data: Continued retention and use of specimens and data is permitted but no further access to data from health records is allowed.
- No further use of the specimen and data: No further contact with the donor is allowed, specimens and data are no longer available to end-users, information from health records is no longer available, and access to health records is discontinued. Remaining specimens and data are to be disposed of according to established repository protocols.
- Restriction from commercial use: The specimen and data may not be used as a whole or part of a process to produce a commercial product.

***BEST PRACTICE:*** The right to withdraw and the process for withdrawing consent should be discussed during the consent process, including details for what to do with specimens and data after participant withdrawal.

### C2.3. Pediatric Assent Process

The collection, storage, and distribution of specimens from pediatric participants creates additional ethical considerations, particularly in gathering informed consent. All implications associated with the use of specimens from adult participants should also be adhered to when working with pediatric participants. These elements include securing ethics review committee approval for all processes and procedures (see *C1.3. Ethical Review*), the minimization of risk associated with participation (see *C2.1. Managing Research Risks for Participants*) and the transfer or disposal of specimen resources (see *Section K4. Transfer and Disposal*). 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.

Subjects below a certain age (which may differ by country or region) are not able to provide informed consent. Instead, parental or legal guardian permission and pediatric research participant assent (in cases where assent may be given) is obtained in lieu of informed consent. To "assent" is to "agree" and the absence of disagreement with the proposed research cannot be interpreted as assent.

The process for obtaining parental permission is similar in intent and content to the process used to obtain informed consent from an adult, with the exception that the documentation contains references to the minor child as the participant. The parental permission documentation should 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 legal guardian to discuss and question the pediatric participant's potential involvement in the research to develop a full understanding.

Once parental permission is obtained, the process of securing pediatric assent may be undertaken if the participant 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 securing parental permission, key topics should be covered with the child, including that they do not have to participate and that they may withdraw their assent to participate at any time in the future (see *C2.2.5. Withdrawal of Informed Consent*).

Until the minor in question is of legal age, parental or guardian permission is required for the minor to participate in research. The age of majority, when individuals are granted the legal right to autonomy by the jurisdictional authority, may trigger a change in consent. Institutional policy on when to transition from using a pediatric assent document to using an informed consent document may incorporate a variety of factors in addition to the age of majority. The process and documentation should be designed with consideration of the emotional, developmental, and cognitive abilities of the pediatric population involved. If the pediatric participants 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 the age of majority is reached if still actively participating in research-related activities. When applicable, provisions for reconsenting can be determined ahead of time within the research protocol, including the mode of communication (*e.g.*, certified letter) and time frame (*e.g.*, within one year after the participant reaches the age of majority). Repositories should take into account any associated costs for re-consenting when initially planning pediatric collections (see *Section A3.2.2. Financial Considerations*). In certain situations, it is possible for

an ethics review committee to determine that the requirements for obtaining informed consent for the now-adult participant can be waived, so reconsenting may not be necessary.

***BEST PRACTICE:*** Appropriate parental permission and age-related assent, compliant with relevant regulations, should be obtained from pediatric participants.

***BEST PRACTICE:*** Repositories should consult with the ethics review committee or applicable institutional authority for guidance on consenting pediatric participants who have reached the age of majority.

## C2.4. Posthumous Biobanking

Many religious and ethnic norms govern the collection of postmortem tissue. Some cultures consider this form of collection to be prohibited and others will permit it under very specific conditions or for certain tissues only. In these contexts, the repository should consult with the affected community and/or seek community consent/authorization for storage, as appropriate. This also applies to human remains stored in museum collections.

Authorization is required to collect and/or use specimens and data from deceased participants, for example during autopsy or for organ donation. Authorization or consent should be obtained from the participant prior to death when possible. Even if authorization or consent was obtained prior to death, authorization may be required from the next of kin and/or a legally authorized representative in accordance with relevant laws. Authorization or consent is similar for pediatric post-mortem collection, including provisions for assent by the minor (as described in *C2.3. Pediatric Assent Process*). Repositories should be aware that the legally authorized representative of a participant can change at the time of death, so it is important to be familiar with the relevant laws.

The repository must consider several key differences in the authorization process for posthumous specimen collection that impact the design, documentation, and solicitation of authorization. One key difference is that many countries do not treat this form of donation under existing guidelines for human research. Even in the case that an individual has given prior authorization (*e.g.*, registration or written advanced directive prior to death), the authorization may be subject to regulations other than standard consent regulations. Another difference between posthumous authorization and standard consent is that withdrawal of authorization may not be permitted, for example in tissue transplant donations.

An autopsy consent may not be required for the post-mortem collection of specimens if otherwise legally consented; however, specimens can be collected at the time of autopsy if specified in either a separate consent to collect them or in the autopsy consent.

Return of human remains may be requested and should be honored wherever possible. Repositories with collections of human remains, *e.g.*, museums or archeological organizations, should treat these collections with the same respect as with modern human collections, including for cultural sensitivity (see *C1.5. Environmental Impact and Biobanking*). Relevant best practices should be consulted for applicable ELSI for biobanking of human remains[32].

## C2.5. Genetic and Genomic Analyses

Medical research involving human genetic or genomic information is important for prevention, early detection, diagnosis, and treatment of different diseases. However, complex ethical issues arise when genetic testing is performed on specimens. The marked progress in genome-sequencing technologies and bioinformatics tools are associated with increased risk of identification of donors, which could breach the efforts exerted by the repository team to protect participant privacy.

With the growth of genetic and genomic research, especially whole-genome research, repositories and participants should be aware of the ethical issues that this research raises. While having great potential to benefit humanity, genetic/genomic research also has the potential to stigmatize individuals, communities or groups, who may experience discrimination, be treated unfairly or inequitably, or suffer other harms based on their genetic information.

***BEST PRACTICE:*** The informed consent process should communicate if genomic sequencing will or may be performed using specimens from the repository, or if genetic information will be shared with genetic/genomic databases.

***BEST PRACTICE:*** The repository should have a genomic data sharing policy that follows applicable local, national, and/or international regulations and guidelines.



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### C2.6. Return of Research Results

Collection and use of human specimens and associated data may generate findings that have implications for the health of the participants/donors and their families. For example, genetic and genomic data may be generated that can detect or predict disease risk. In addition, other types of data collected or generated by the repository or through use of specimens, such as clinical testing data, or proteomic data could have implications for participants and their families. However, return of research results and incidental findings (information discovered during the research beyond the aims of the research) to participants and their biological relatives can be ethically challenging.

There may be ethical obligations to return results to participants in some circumstances, such as when results indicate a serious health risk that can be mitigated. There may be risks to participants from the return of individual research results that have not been analytically and clinically validated, or the significance of which may not be clear. These risks include emotional distress due to the significance and impact of such findings (*e.g.*, if results are associated with any familial or stigmatizing disease) and potential harms from treatments based on inaccurate findings (see *C2.1.3. Psychosocial Risk*)[15].

In addition, there may be practical implementation issues that make the return of findings complicated and/or difficult[46]. For example, the repository may not have a direct or ongoing relationship to the research participants and the passage of time between collection and use of specimens and/or associated data may add to these challenges. Furthermore, return of results may require considerable resources, including costs for locating participants, validating research findings, and securing the necessary expertise to ensure that results are returned in an ethically responsible way.

Repositories should give careful consideration to all issues when developing strategies whether and how to return research results.

- Results to be returned to individual participants should have both:
  - Clinical validity, *e.g.*, strong evidence of the correlation with a disease or condition.
  - Analytical validity, *e.g.*, proven through a reference method[47] (see *Section D3.6. Validation, Verification, and Qualification*).
- It is also possible to share aggregate research findings with the communities from whom the specimens and associated data were obtained. This may be accomplished through the use of newsletters, posting summaries of research made possible from the collections on the repository website, etc.
- Some countries have laws and regulations that require the return of research results under certain circumstances (see *C1.2.1. Compliance*).

Thus, it is advisable to discuss these issues with the ethics expertise available to the repository, *e.g.*, ethics advisory board (see *Section A2.2. Governance Structure*) before developing the policies (see *Section A2.4. Policy Development*).

A policy for return of research results should in place that addresses what (if any) results are returned and to whom (*e.g.*, participant and/or genetic relatives); how participants are contacted; the process to follow if re-contact is not possible; any support available (*e.g.*, from a genetic counselor); and options to decline receipt of research results, even after initial agreement to receive these. The policy should additionally describe how to handle the discovery of serious and significant findings uncovered either directly within the scope of the research or incidental to the research that has significant health implications for the participant and/or their genetic relatives. The process should be explained to participants during the informed consent process.

Approval by an ethics review committee (see *C1.3. Ethical Review*) should be in place before attempting to return any research results to participants, their families, or physicians.

Repository personnel should be trained and deemed competent (see *Section E. Training and Competency*) to understand who has consented to receive findings, what information will be returned, and the methods of returning results. Additionally, repositories should ensure that adequate resources are available to support return of research results in an ethically appropriate and meaningful way, such as counseling and/or clinical expertise[46].

***BEST PRACTICE:*** The repository should have an ethically approved policy in place that governs if and how research results are disclosed to participants. This policy should be shared and discussed with potential participants during the informed consent process.

***BEST PRACTICE:*** Repositories that return research results should secure the necessary expertise and resources to effectively communicate the findings and any subsequent implications (*e.g.*, medical intervention) to research participants and their families, or to the participant community if applicable.

## C3. ELSI FOR MICROBIAL SPECIMENS AND DATA

### C3.1. Collaboration and Harmonization to Enhance Capability

Different initiatives have been launched to support end-users giving them access to specimens and associated data that are fit for purpose, as well as to expertise focused on ethical and legal liability.

A primary international effort is the Convention of Biological Diversity (CBD) dealing with sustainable development and intellectual property rights that has given rise to the Nagoya Protocol[10]. The Protocol establishes obligations to harmonize collaboration among member parties, including requirements to obtain Prior Informed Consent, establish Mutually Agreed Terms, and facilitate fair and equitable benefit-sharing with the provider countries and communities before embarking on any fieldwork (see *C1.2. Legal Implications*).

Globally, a number of networking activities exist specifically to promote collaboration to increase the accessibility of microbial specimens and data, as well as facilitate sharing of knowledge and expertise for harmonizing microbial strain information, quality management and legal issues[48]. Examples include: World Federation for Culture Collections (WFCC)[49], European Culture Collections' Organisation (ECCO)[50], United States Culture Collection Network (USCCN)[51], Asian Consortium for the Conservation and Sustainable Use of Microbial Resources (ACM)[52], and European Consortium of Microbial Resources Centres (EMbaRC)[53]. The pan-European Microbial Resource Research Infrastructure (MIRRI-ERIC)[54] focuses on aligned goals supporting research and development in academia and industry. Such microbial resource networks generally encourage support for and promote the deposition of microorganisms and genetic materials such as recombinant plasmids for accessibility.

Examples of some resources on legal matters include:

- TRUST (TRansparent User-friendly System of Transfer) produced by the Belgian Science Policy Office[55]: TRUST is developed in cooperation with the World Data Centre for Microorganisms[56] via the Global Catalog 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 work of microbiologists[57].
- The Best Practice Manual on Access and Benefit Sharing issued by MIRRI-ERIC[25] 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 may conduct research on their holdings and utilize genetic resources and associated traditional knowledge.
- ECCO has produced models of material deposit and transfer Agreements[58] (see also *Section K3. Transfer Agreements*) that may be useful globally.

### C3.2. Biorisk Management

Repositories handling microbial collections should be aware of concerns related to the potentially devastating risks posed by dispersal of biological agents and toxins. To assist in enforcing national and international efforts to safeguard from such threats, repositories should have the necessary tools and resources (policies, procedures, restricted access, etc.) to foster a biological secure culture in accordance with their collection types and activities. Considerations to promote such a culture include[59]:

- Sharing with personnel and end-users the risks and threats associated with biological agents and toxins.
- Documenting the repository responsibilities and efforts to protect against both deliberate and unintentional misuse, including training personnel to operate safely and securely.

Biosafety and biosecurity are complementary approaches to managing these risks. Biosafety aims at protecting the society and environment from accidental exposure to biological agents, whereas biosecurity focuses on institutional and personal security measures and procedures designed to prevent intentional release of hazardous biological resources. Prevention is aided by ensuring management commitment, accountability, and transparency and enabling capacity for surveillance, detection, and response and recovery.

The relevance of biological security challenges may not be immediately apparent[60]. In particular, repositories responsible for microbial collections should be aware of the need to guard against downplaying the threat when assessing risks (see *Section B. Risk, Emergency, and Disaster Management*) in the management of dual-use research of biological agents. Repositories should routinely review and revise its biorisk management approach, including evaluating policy alternatives; considering risk assessment and other factors relevant for biosecurity; and implementing appropriate prevention, containment, and response techniques (see *Section F4.1. Biorisk Management*).



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Relevant national and international guidelines[61-63] recommend the adoption of appropriate biosecurity measures to protect from unauthorized access, loss, theft, misuse, diversion, or intentional release.

***BEST PRACTICE:*** Repositories should routinely assess biorisk and implement appropriate biosafety and biosecurity measures in line with the type and purpose of the repository and the nature of the collections.

## C4. ELSI FOR ANIMAL SPECIMENS AND DATA

All processes and procedures for the collection, processing, storage, distribution, and use of specimens from animal donors should receive prior approval from an ethics committee, such as an Institutional Animal Care and Use Committee (IACUC) in the United States or the Animal Welfare and Ethical Review Body (AWERB) in the United Kingdom. Different guidelines may apply for archeological materials, *e.g.*, museum collections, and repositories should consult international and regional regulations, laws, guidelines, and best practices where available[32].

### C4.1. Consent Process

Animal collections should follow the same informed consent regulations as those for human specimens (see *C2.2. Informed Consent Process*), making sure the information is clear to the animal's legal representative (*e.g.*, owner). Broad consent and specific informed consent (for immediate research use) are most often used in veterinary hospital collections. As described in *C1.5. Environmental Impact and Biobanking*, additional considerations apply when collections pertain to indigenous lands.

### C4.2. Ethical Treatment of Animals

The Replacement, Reduction and Refinement (3Rs) principle can be applied to all repository activities, including collection of animal specimens to help minimize animal use and suffering and to facilitate good scientific practice[64]. Where feasible, alternative insentient methods and procedures should be used in preference to using animals. When animals are used, the numbers should be minimized and efforts should be undertaken to minimize adverse effects and to maximize the scientific benefit gained[32]. The 3Rs underpin many of the animal research regulations and legislation in force in various regions and countries throughout the world.

Efforts to harmonize procedures among animal repositories aim to minimize or eliminate pre-analytical confounding variables, and the resulting compatibility of studies, that can result in a reduced number of animals used for experimental research. Such harmonization can result in improved animal welfare practices for the benefit of both animal donors and science.

If collection is undertaken by the repository, the "five freedoms" concept, first presented by the British Farm Animal Welfare Council[65] as general indicators of animal welfare to support the implementation of the 3Rs principle, is of key consideration. 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.

(5) Freedom from fear and distress.

In any animal resources facility, personnel should implement actions to minimize the impact of the procedures they perform according to these five freedoms.

Repositories should establish guidelines for accepting postmortem specimens from euthanized animals, which may include reviewing laboratory/institution euthanasia protocols. To support ethical treatment of animals, euthanasia methods should:

- Achieve rapid unconsciousness and death.
- Require minimum restraint.
- Avoid excitement.
- Be suitable for the age, species, and health of the animal.
- Minimize pain, fear, and psychological stress in the animal.

- Be reliable, reproducible, irreversible, and simple to administer.
- Be safe for the operator.

Rodent and other animal models, especially porcine models due to their physiological and metabolic similarity to humans, are used extensively to support translational research. From an ethical and cost perspective, a critical factor in collecting specimens from euthanized individuals is to maximize distribution and use of the specimens and the associated data. Repositories should follow guidelines, where available, for generating representative specimens and data from different model organs and tissues, to avoid underuse of the animal.

### C4.3. Safe Animal Handling and Transport

Repositories that collect from multiple distinct species should be aware of any sanitary restrictions or legislation (*e.g.*, to prevent cross-species transmission of diseases) that impact the activity of collecting specimens. Appropriate solutions should be implemented where required (*e.g.*, separate areas for collecting of semen and oocyte from different species). An animal health certificate should be provided with the distribution of such specimens. The Terrestrial Animal Health Code of the World Organization for Animal Health[66] regulates standards to detect and protect against spread of zoonotic agents during movement of specimens. Some geographical regions have further national or regional legislation further relating to this.[67]

***BEST PRACTICE:*** To ensure the ethical and legal collection of animal specimens for research, repositories should refer to relevant international and national regulations and legislation and any applicable local animal care and use policy. Measures to minimize animal use, as well as pain and distress, should be undertaken.

## C5. ELSI FOR PLANT SPECIMENS AND DATA

Plant-sourced specimens and associated data are collected for a number of potential research uses, including agricultural and medical research. Plant collections may encompass numerous biological specimen types, including frozen plant tissues, fluid-preserved plant tissues or associated extracts, seeds, extracted nucleic acids, and relevant associated data. To maximize the potential benefits, and reduce potential negative impacts of the collection, the repository should strategically design the processes for plant collection and accession management to ensure fitness for purpose (see *Sections D1. General Introduction to Quality Management* and *D3.5. Quality Control Approaches*) and cover regulatory issues. Many repositories that curate plant material focus on plant interactions with other species and should be aware of practices pertaining to handling and management of the relevant species. A plant repository obtains its accessions in different ways, *e.g.*, from donors (principally researchers or breeders), by collecting from in situ/native habitats, and through exchange with other plant collections. Archeological materials, *e.g.*, museum collections, may include plant specimens which should be preserved according to archeological ethical best practices[32].

### C5.1. Specimen Acquisition

The acquisition of seeds and other plant parts (see *Section J4. Collection Considerations*) should comply with relevant international and national regulations, including the International Treaty on Plant Genetic Resources for Food and Agriculture[11] or the Convention on Biological Diversity access regulations[10]. Acquisition practices should consider relevant guidelines for limiting collection, such as the Food and Agriculture Organization (FAO) practical guide on conservation[68] or the European Native Seed Conservation Network (ENSCONET) collection manual for wild species[69]. As described in *C1.5. Environmental Impact and Biobanking*, additional considerations apply when collections pertain to indigenous lands.

Where feasible, a repository should advocate leaving enough of each plant or an adequate number of seeds or propagules to allow for regeneration. Whole wild plant collection should be avoided for vulnerable populations. The plant repository should monitor restrictions on collecting species that are threatened, endangered, sensitive, or otherwise of special concern. There may be specific locations or occasions where collection is prohibited or where seasonal or other restrictions apply, *e.g.*, for diseased or stressed populations. Repositories can consult the International Union for Conservation of Nature and Natural Resources (IUCN) Red List of Threatened Species[70] as an indicator of the global conservation status of species of interest including fungi and plant species. This tool may inform the adoption or alteration of appropriate practices for biodiversity conservation.



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Where circumstances may result in severe threat or disappearance of the plant genetic resources in situ (*e.g.*, planned development of an area, exposure to a devastating disease), salvage of those plants or plant populations for static ex situ biobanking or other collection may be appropriate where authorized by the landowner or administrator.

A repository should evaluate and document the impact of collection, to justify (further) collection.

The repository should be aware of and fulfill, as applicable, any criteria specified as part of the authorization to collect in a different country/geographical region. Criteria may include the following benefit sharing practices among others:

- Deposition of duplicate isolates of newly described plants at in-country institutions.
- Inclusion of an in-state or in-country scientific collaborator (*e.g.*, an existing expert) to avoid exploitation of plant genetic resources.
- Involvement of in-country personnel (*e.g.*, graduate student) in the process as a commitment to sharing of expertise (often funded at the expense of the repository; see *Section A3.2.2. Financial Considerations*).
- Acknowledgement of in-country as source of the plant specimen and associated data, and other in situ assistance, biobanking assistance, permit handling, etc. (see *C1.4.1. Benefit Sharing*).

## C5.2. Safe Handling and Transport

Repositories should have systems in place to protect the genetic integrity of the surrounding native species and natural vegetation while collecting. When collecting and handling non-native species, personnel should use accepted precautionary measures to prevent seed or propagative plant parts escaping from the collection. The repository must adhere to regulations and guidelines regarding the transport of plant specimens, ensuring compliance with the laws of all regions through which the material travels. Additionally, the Convention of International Trade in Endangered Species of Wild Fauna and Flora (CITES)[13] regulates import, export, and re-export of IUCN-listed endangered species and derived materials (see *Section L. Packaging and Shipping*). International and regional treaties, including the Nagoya Protocol[10], may also govern the transport and transfer of plant specimens.

## C5.3. Voucher Specimens

Where verification of specimen identity is a criterion, plant specimens should be referenced against a voucher specimen (see *Section D3.5.5. QC for Plant Specimens*). If a plant voucher is not already available (*e.g.*, as part of a national collection), the repository should consider establishing a voucher specimen for its collection. Vouchers should be permanently maintained and accessible as part of a stable collection[71].

A population or species can be vouchered either as a whole plant, in sustainable populations, or a plant part. An image, *e.g.*, photo documentation can be used when no plant parts can be collected. In this setting, the characteristics (*e.g.*, morphological) of the plant should be clear and sufficiently detailed to assist in unequivocal species identification.

Physical vouchers should be taken only where the source population suffers no irrevocable harm. With rare species under investigation, voucher material should be removed judiciously, minimizing damage to the plant and its habitat. Permits obtained from authorized personnel should be in place prior to collecting, and the repository may need to account for authorization of named personnel to participate in collecting or to provide materials.

It is important for publications that address the collection, banking, and distribution of plant specimens to include a voucher for each referenced population to authenticate their findings. Information regarding where to access these vouchers (*e.g.*, museum, university) enhances the scientific value of a publication, not only by addressing accurate taxonomic information but by allowing other investigators to explore the resource and examine the associated metadata. Derivatives from banked biospecimens (*e.g.*, nucleic acids) may complement a voucher and lead to more accurate findings that can be replicated in future studies.

***BEST PRACTICE:*** Repositories should limit collection of plant material considered vulnerable, of special concern, or from rare habitats, *e.g.*, wetland, desert wash, and groundwater-dependent communities. Wild plant collection should not result in a loss of population viability.

***BEST PRACTICE:*** Wild plants should never be collected unless authorized by the landowner or administrator, and by relevant regulatory bodies with responsibility for biodiversity and environmental protection and disease prevention.

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# SECTION D: QUALITY MANAGEMENT

## D1. GENERAL INTRODUCTION TO QUALITY MANAGEMENT

Quality is the degree of suitability of inherent characteristics to meet or fulfill requirements for an intended purpose. Quality is fundamental to a repository's operation, purpose, and mission and should be planned for and managed. Quality management (QM) should address any component or activity that impacts on the quality of a specimen and its associated data. The quality criteria associated with the use or purpose of a collection should be defined by the repository and may be influenced by end-users (where known) or by multiple parties. Specimens and associated data that meet these quality criteria are considered fit for purpose (FFP), enabling effective and reliable research for that purpose. Specimens and data deemed fit for one purpose may not meet quality criteria for all purposes, necessitating evaluation against additional or alternative criteria to establish fitness for alternative purposes. In this context, QM is a continuous undertaking by which a repository can assure and evaluate quality to facilitate access to specimens and associated data that are fit for purpose.

A quality management system (QMS) integrates policies and practices for the full spectrum of quality in a repository. A QMS can be used by a repository to document policies, processes, procedures, and responsibilities to ensure that the specimens and data comply with applicable regulatory and ethical requirements as well as any quality specified criteria. A repository should evaluate risks and opportunities as part of a QMS, or QM program. QMS includes continual improvement based on generally small, ongoing, and well-calculated changes that lead to significant improvement over time. A QMS can be facilitated manually, *e.g.*, with paper-based documentation, supplemented by electronic systems, or be entirely based on a software solution, according to the resources available to the repository.

Quality assurance (QA) contributes to a robust QMS and focuses on quality of the repository processes. QA is an integrated approach to make sure that processes are of the type and quality needed. QA is proactive and aims to prevent issues within processes that could impact the fitness for purpose of specimens and data. A QA program typically involves planning, implementing, assessing, and improving. It is supported by documentation focused on providing evidence that quality requirements are met. Continual improvement and resolution of issues comes through cyclical repetition of these actions.

Quality control (QC) is complementary to QA and verifies FFP of specimens and associated data. QC is reactive and intends to verify whether quality requirements have been met by monitoring the occurrence of unexpected results. It acts on the process outputs (generally specimens and associated data), but QC can also be applicable to an input of a process, aiming to verify the influence of the process on what is being processed. For example, QC can be used to confirm the authenticity of reference strains, to verify the viability and purity of cell lines before and after freezing, or to identify errors in data migration between computer systems.

Repositories should establish and document what quality means for (the different) specimen types and associated data in terms of FFP. Definitions of quality criteria include regulatory, ethical, analytical, and other requirements, and should include range limits that if exceeded render specimens and associated data unfit for purpose.

Of the potential errors associated with specimens and data for research, a number may accumulate during the preanalytical phase. A repository should design QA processes to minimize errors during the handling of the specimens and data and then use QC testing to check for specific indicators of biological activity or other critical preanalytical factors (*e.g.*, for specimens: minimum amount and/or volume, identifiability, and association with key data variables).

***BEST PRACTICE:*** The repository should be able to demonstrate a commitment to management of quality throughout core (critical) operations through documented quality assurance actions.

## D2. QUALITY MANAGEMENT ROLES AND RESPONSIBILITIES

Overall responsibility for quality management planning, implementation, and routine review should be assigned to the Director and/or designee (*i.e.*, Quality Manager). A variety of third-party stakeholders may influence quality management. Stakeholders may include:

- Committees or review boards: These may have specific guidelines and responsibilities that need to be followed (see *Sections A2.2. Governance Structure* and *C1.3. Ethical Review*). QM considerations from these bodies may serve as recommendations, guidance, or as requirements for participation and may influence the frequency and structure of reporting. In some cases, QMS records may be shared publicly or otherwise made visible to inspectors and community members outside of the repository.
- Sponsors/funding bodies: Each sponsor may have specific requirements, *e.g.*, procedures, clinical trials, reporting, long-term viability of repository, publications, federated collections.


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- Government or regulatory agencies: Many agencies require application of specific controls for handling of certain specimen types, *e.g.*, pathogens, genetically modified organisms, therapeutics, blood products, cellular and tissue-based products. External auditing (see *D3.7.2. External Audit*) and corrective actions (see *D3.8.2. Corrective and Preventive Actions*) may feature. Non-compliance may result in disciplinary action or monetary penalty. Agencies may require quality management to be aligned to quality standards, such as ISO 9001[1] (see *D4.2. Standards*). Regulatory involvement may include maintenance of records, deviation reporting, and identification and traceability (see *D4. Resources for Quality* and *Section C1.2. Legal Implications*).

It is the responsibility of the Director/designee to assess the perspectives of stakeholders, and to ensure that quality is managed to meet relevant regulations, standards, guidelines, and any contractual obligations. Personnel in all roles should be trained in quality management. All personnel should exercise collective responsibility for assuring compliance within quality management. Fostering a culture of reporting of quality issues by personnel should be encouraged as opportunities to learn through experience. This can be achieved by implementing a proactive, positive approach for addressing quality issues.

A repository should define the responsibilities for all quality roles including auditing, non-conformities, deviations, and any accreditation or certification processes (see *Section A2.3. Governing roles and Responsibilities*, Tables A1 and A2). To ensure consistency, training and competency assessment programs should be established as an important component of quality management (see *Section E. Training and Competency*).

***BEST PRACTICE:*** A structured process for reporting of issues for quality improvement should be established and made readily available to personnel.

## D3. QUALITY PLANNING

Quality Management in a repository is a set of linked activities used to manage, direct, and improve quality. The repository should have a quality management policy in place to manage the direction of repository quality and should plan for all aspects of quality such as quality assurance, quality control, and quality improvement. A key element of quality management is the documentation of information.

### D3.1. Quality Manual

A repository should develop and maintain a quality manual (may be called an alternative term such as quality plan) which contains procedures, instructions, and guidance for use by repository personnel. The quality manual describes the framework in place for quality management (specifically the QMS for many repositories) and includes information about the organization, its goals, and its policies. It is one of the central documents of quality management. The quality manual should be readily accessible to repository personnel and may include the following:

- Quality statement.
- Policies (see *Section A2.4. Policy Development*), *e.g.*, relating to administration; documentation; personnel; quality management; ethical, legal, and social implications (ELSI); access for use; financial sustainability; data management.
- Organizational chart, including director and personnel responsibilities and delegation of functions.
- Plans for:
  - Repository governance (see *Section A2. Repository Governance*).
  - Operations (see *Section A4.4. Operations Plans*).
  - Health and safety (see *Section F. Health and Safety*).
  - Training (see *Section E. Training and Competency*).
  - Risk management (see *Sections B. Risk Emergency and Disaster Management* and *I3.14. Data and Systems Backup and Disaster Recovery*).
  - Data management (see *Section I2.1. Data Management Plan*).
  - Communication (see *Section A5. Communication and Repository Promotion*).
  - Facilities and equipment management and security (see *Sections G. Facilities* and *H. Storage and Processing Equipment*).

The quality manual may make reference to the existence of:

- Procedures, specifically standard operating procedures (SOPs)
  - » Specimen and data handling (*e.g.*, collection, accession, labeling, transport, receipt, quality control, processing, testing, distribution, shipping, and disposal.
  - » Specimen inventory and tracking (see *Section J8. Specimen Inventory Management*).
  - » Validation, verification, and qualification of instruments, reagents, labels, processes, and systems (*e.g.*, monitoring, alarm alert, and response) used in specimen and data collection, processing, storage, and retrieval (see *D3.6. Validation, Verification, and Qualification*).
  - » Quality metrics, handling non-conformities, performing corrective actions.
- Templates *e.g.*, for access and sharing of specimens and associated data (see *Section K3. Transfer Agreements*).
- Auditing (see *D3.7. Auditing for Performance Review*).

## D3.2. Documentation Management and Control

Information within a repository needs to be documented, managed, and controlled, and can be collectively termed as *documented information*. Documented information includes both documents and records. Documents typically pertain to information necessary for repository operations, management, and governance, whereas records provide long lasting, traceable evidence of actions taken and results obtained at specified time points (see ISO 9000:2015 Quality management systems — Fundamentals and vocabulary for related definitions[2]). A form (*i.e.*, a document) becomes evidence (*i.e.*, a record) once it is filled in.

Documented information can be in any manual and/or electronic format or media and from any source. Documentation management involves the reception or creation, revision, review, authorization, publication, and archiving or disposal of documents and records, in a systematic (*i.e.*, planned) and consistent (*i.e.*, same treatment) manner. Documented information should be controlled as part of document management to assist with organization of information and to improve efficiency within the repository. A document control policy may also be prescribed by the parent organization, and the repository documentation management and control practices should be aligned to any such policies.

***BEST PRACTICE:*** Repositories should control and manage all documented information comprising documents and records.

***BEST PRACTICE:*** Repositories should develop a complete record management system to track all repository operations.

### D3.2.1. Creation of Documented Information

Many different types of documented information are received, created, and used within a repository (see *D3.1. Quality Manual*). The creation of documents should be performed in a systematic and controlled manner, *e.g.*, by establishing standardized processes to clearly communicate information. A repository can develop a variety of documents, including template forms and spreadsheets to allow for effective tracking and monitoring of repository activities and operations. Documents should be uniquely identifiable (*e.g.*, using a unique number), have a distinct title, and include relevant date(s), *e.g.*, when the version was created, revised, approved (*i.e.*, version tracking). Other elements might include a change history section (see *D3.2.5. Changes to Documented Information*). For a specific example of a document creation, see *D3.3. Standard Operating Procedures*.

Records should reflect information pertaining to activities such as: personnel training and competencies, informed consent, procurement, processing, assay reports, equipment maintenance (including equipment operations and repair, nonconformity, or incident reports), audit/review reports, specimen storage location information, contracts, specimen and/or data distribution, and monitoring/alarms. Records should be created and information documented and maintained in a manner that allows steps to be traced and to enable a chain of custody.

To reduce risk when using paper forms to produce records, the following is recommended:

- Inclusion of version number and date, form name or identifier, and page numbering, with final page identification and space for initials and date.
- Inclusion of specific instructions, *e.g.*, conditional recording, date formats, and roles and/or responsibilities for completing and signing off.
- Use of binding that reduces risk of page loss or order discrepancy.
- Use of specified ink color and legible handwriting to facilitate clear documentation.



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When recording date and time, the use of the dating convention in place should be carefully considered by the repository when recording the interactions with specimens and/or data, including distribution to end-users. While an international standard (ISO 8601:2000 Date and time — Representations for information interchange[3]) exists for writing calendar dates for international communication presented in a descending order of year (4 digits), month (2 digits), and day (2 digits), *i.e.*, YYYYMMDD, a repository might already use a different dating convention. It is advisable for a repository to be unambiguous in its communication, by specifying the dating convention used along with the specific date and time.

***BEST PRACTICE:*** Forms or spreadsheets to record the most important data (*e.g.*, participant consent or source data) that correspond to the procedures that may impact on quality of the specimens should be developed and maintained in the repository's data management system (see *Section I2.2. Data Management System*).

***BEST PRACTICE:*** Documented information should support consistent and reliable tracking, *e.g.*, through definition of formats, structures, and level of detail required.

### D3.2.2. Storage and Retention of Documented Information

A repository should use strategies to safeguard (*e.g.*, retain copies of critical paper records, regular backup of electronic documents and records, storage within a secure location with access control, etc.) against:

- Loss, including loss of legibility.
- Any intentional or unintentional use or disclosure that compromises confidentiality and biosecurity.

Unless otherwise specified by contract, corporate or government policy, or other agreements, the repository should specify the retention time of each type of documented information within its policies (see Retention Time in *Section A1.1. Types of Repositories*). Additionally, the repository's documentation management policy should indicate how records that are no longer needed should be destroyed or transferred (see *Section I3.10. Reporting from IMS*). For example, equipment maintenance and repair records can be archived following retirement of the equipment.

Continued retention of documented information for collections that are no longer active, such as those in closure phase (see *Section A1.2. Lifespan and Phases of a Repository*), or for specimens that have been destroyed or transferred from the repository depends on the type of repository, the documentation management policy in place, and any other relevant requirements. Certain requirements (*e.g.*, of funding or regulatory bodies) might stipulate the retention of information pertaining to inactive collections or specimens that have been removed from the repository for tracking and documentation purposes. For example, signed informed consent forms linked to a specimen are to be retained for many years, and for natural history collections, data records (and to the extent known, all other data categories related to the use of the specimen) should be stored indefinitely, unless otherwise dictated by the agreements with the country of origin.

Security and confidentiality of stored documented information should be addressed within the data management plan (see *Section I2.1. Data Management Plan*). Privacy and confidentiality should be actively managed using appropriate controls (see *Section I2.3. Data Security and Privacy*, and *I3.13. Data Security for Inventory Management Systems*) for compliance with data regulations pertinent to the regions of collection and for future use.

***BEST PRACTICE:*** Repositories should define the storage conditions and the time for retention of documented information consistent with its needs and contractual and legal obligations.

### D3.2.3. Retrieval and Availability of Documented Information

Documented information should be easily accessible and saved in an electronic shared file system (*e.g.*, inventory management system [IMS], see *Section I3. Inventory Management System*), where practicable. Access to documented information should be on a need-to-know basis. Records and other documentation should be readily available for inspection by authorized personnel from regulatory agencies (*i.e.*, those with jurisdiction over such activities) and quality assurance personnel. Access to privacy records or confidential client information should be restricted to repository personnel authorized to grant access to inspectors from regulatory agencies and other approved auditors. If digital forms become temporarily inaccessible, the repository should have a system in place for recording the information in a way that is deemed acceptable (*e.g.*, use of a hard copy form to be uploaded at a later point).

### D3.2.4. Review of Documented Information

To ensure relevance to the repository quality objectives, policies and processes, documented information should be evaluated within a review process, including any editing for revision, and finalizing including approval. A

proactive approach to review ensures the documented information continues to align with the evolving needs and requirements of the repository. A repository should undertake regular and routine reviews of documented information to maintain relevance and effectiveness. In addition, documented information should be reviewed promptly to identify the necessary updates or corrective actions in response to accidents, incidents, or after identification of QA/QC non-conformance.

Document revisions should be performed by personnel possessing the appropriate expertise related to the process being documented (*e.g.*, technical expertise for SOPs). The content of the document should be reviewed by a competent person who is not the original author/reviewer, where practicable.

Any revisions to documented information should be appropriately and completely logged to ensure transparency.

***BEST PRACTICE:*** The repository should establish regular reviews of documented information and consider an increased frequency for review of documents that directly impact on fitness for intended purpose.

#### D3.2.5. Changes to Documented Information

Documents can be revised and improved over time, whereas changes to existing records should be avoided, unless justifiable as records provide evidence that reflect activities and results at specified time points.

Each time a document (*e.g.*, policy, form, or SOP) is changed or revised, a record of the change should be kept, for example, within a dedicated change history section. The change history is updated when a new version is created. The new version should be approved by responsible personnel before use. A system should be in place to ensure that only current versions of documents are available for use and that previous versions are removed and archived when new revisions are issued.

Accurate recordkeeping enables compliance with relevant legal and ethical requirements (see *Section C1.2.1. Compliance*) and is key to a repository's trustworthiness (see *Section C1.1. Ethical Principles and Recommendations*). Changes to existing records (*e.g.*, assay result, correspondence, or signed informed consent) should only occur when justifiable. A procedure should be established if corrections to records are deemed acceptable. A repository might find the inclusion of a list of record change justifications useful. Justified corrections or amendments (changes) to an existing hard or soft copy record should be evident with the original entry still legible/traceable. The change should be trackable to the individual making the change as well as to the date and time of the change (see *D3.2.1. Creation of Documented Information*). The reason for the amendment should be added. Use of an IMS that can maintain an audit trail is recommended.

***BEST PRACTICE:*** Personnel should be trained and deemed competent to produce records that are accurate, complete, and legible, and follow the established documentation practices.

### D3.3. Standard Operating Procedures

An SOP is a written document with a detailed description of all steps required to carry out a repository operational task. The main objective of an SOP is to facilitate uniformity of repository processes so that errors, deviations, and variation are minimized and to ensure reproducibility in specimen and/or data handling and preservation.

***BEST PRACTICE:*** The repository should have SOPs in place with detailed description of how to carry out tasks pertaining to critical repository operations, including life cycle stages. SOPs should additionally be reviewed and/or revised when policy or methods change (see *D3.2.4. Review of Documented Information*).

#### D3.3.1. Potential components of an Standard Operating Procedure

An SOP should be written by personnel with experience in successfully performing the activities described. Format and structure of SOPs can vary widely. Organizational instructions to write an SOP, which may include institutional templates, often exist and should be used where relevant. Several templates and examples of repository SOPs are publicly available[4-6]. Generally, components of an SOP include the following:

**Administrative:**

- Title: A unique name which captures the essence of the procedure described.
- Identification: A unique acronym and/or number that can be used for easy reference.
- Date: Date that the SOP becomes effective.
- Version Reference: Number of the most recent approved version in place.
- Page Numbering: Number of the page and total of pages.


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- Authorization: Names and/or positions of the reviewer(s) and approver(s) of the version.
- Revision History: Summary of changes that have been made over versions.

**Main Content Outline:**

- Scope: Department/division/personnel/process to whom the SOP applies.
- Aim: Description of the intent of the SOP.
- Terms and definitions: Specific terms used in the SOP with their definitions to ensure the correct understanding by readers.
- Process: Detailed description of activities to be performed in a logical sequence. Examples include timing of steps, temperatures and/or any other specific environmental condition at which the steps are to be performed, quality control activities, instructions for labeling, assigning unique identifiers, packaging specimens, etc.
- Resources: Everything needed to perform the operational procedure, including health and safety information such as relevant personal protective equipment (see *Section F3. Personal Protective Equipment*), equipment, supplies of reagents, and consumables.
- Related Documents and Appendices: Documents, forms, diagrams, flowcharts, pictures, etc., related with the SOP and which need to be used, followed, or consulted.

**Additional Content:**

- References: Documentation interfacing with the SOP, *e.g.*, related versioned SOPs, manuals, publications, and regulations.

#### D3.3.2. Standard Operating Procedure Access

SOPs are intended for those who perform a specific task and should be simple, complete, and objective enough for relevant personnel to comprehend. The repository should ensure that the personnel responsible for carrying out operational tasks have access to the latest authorized versions of all task-related SOPs. The latest versions of all SOPs should be maintained in designated locations and always be available to responsible personnel[7].

Personnel should be adequately trained in all SOPs related to their roles and responsibilities. Completion of such training as well as any competency assessment should be documented in a training record (see *Section E. Training and Competency*).

#### D3.3.3. Implementation

The repository Director and/or their designee should approve all SOPs and associated process validation studies prior to implementation. The accepted version should be signed either electronically or manually. Upon implementation, all SOPs should be followed as written and controlled in a document management system (see *D3.2. Documentation Management and Control*).

## D3.4. Quality Assurance Approaches

#### D3.4.1. Specimen Quality Assurance

Policies and procedures should be in place to maintain specimen and data integrity (see *Section J3. Specimen Integrity*) for all steps from collection/reception to distribution, considering the potential end-use to ensure FFP. Specimen quality assurance approaches can encompass any processes or tool (*e.g.*, qualification of equipment, methods validation, audits) used to ensure that the specimen quality criteria will be fulfilled.

Using validated processing methods that focus on the reproducibility and the robustness of the method, among other criteria, is a key point to assure the quality of specimens (see *D3.6. Validation, Verification, and Qualification*). It is also important to consider the influence of preanalytical variables (*e.g.*, temperature, time) on the integrity of the specimen that could negatively influence the specimen's quality. Controlling preanalytical variables can be challenging; recording the information related to all stages of specimen handling can help assess specimen quality and FFP (see *D3.6.3. Preanalytical variation*).

Specimen quality assurance can be additionally supported by an external quality assurance program; for example, the performance of specimen processing or accuracy of specimen testing can be assessed externally either by a peer group of repositories or by a reference laboratory (see *D3.4.3. External Quality Assurance*).

Periodic reviews of specimen quality issues and adjustments to the approaches used can help to ensure continual quality improvement.

***BEST PRACTICE:*** Repositories should have specimen quality assurance policies and procedures in place. These should include, but not be limited to, validation of specimen processing methods; documented information of specimen collection, processing, and storage; audits; and other approaches to ensure that the agreed specimen quality requirements are fulfilled.

### D3.4.2. Data Quality Assurance

Policies and procedures should be in place to maximize accuracy and completeness of data (see *Section I3.12. Data Entry*). These should include data monitoring mechanisms enabling detection of missing or incomplete data (*e.g.*, verification or validation of data such as regular checks of data type, range, and consistency) and resultant corrective action strategies. Reviews of data quality should be periodically undertaken including when adjustments are made to programs/software and data handling processes contributing to continual quality improvement.

Similarly, where an IMS is used (see *Section I3. Inventory Management Systems*), the quality assurance approach should be focused on prevention of non-conformities and process improvement. Elements of IMS quality assurance can include:

- Ensuring that data elements are relevant and fit for purpose.
- Meeting IMS-user criteria, *e.g.*, sector-specific certification.
- Assessing software functionality against IMS-user criteria.
- Identification of data errors and modifications.
- Using corrective action strategies.
- Personnel training and competency assessment for IMS use (and IMS development, where applicable).

***BEST PRACTICE:*** Data quality assurance should be sufficient to address downstream applications and incorporate improvements over time with feedback (*e.g.*, for quality control, end-users etc.).

### D3.4.3. External Quality Assurance

Participation in external quality assurance (EQA) programs where repository performance is evaluated through inter-laboratory comparison provides another layer of confidence to end-users. EQA determines the performance of individual repositories for specific processes. It can be used as a tool to monitor the integrity of repository results and to monitor continuing performance over time.

Performance of methods can be assessed indirectly by evaluating performance in processing, producing, and storing of specimens relative to metrics collected by a central laboratory. The central laboratory produces an average (*e.g.*, DNA yield or ratio) obtained from all participating repositories and assesses the performance of each participant relative to others. This evaluation is notably performed with respect to challenging materials (*e.g.*, DNA or RNA extracted from formalin-fixed paraffin-embedded [FFPE] tissues). EQA allows a repository to evaluate the accuracy of its specimen testing methods by comparing results with other repositories.

Proficiency testing (PT) as an EQA option is taking on an increasingly prominent role in repositories (*e.g.*, ISBER-endorsed BioRepository Proficiency Testing Program[8]). It can be used to identify interlaboratory differences and issues relating to personnel performance or calibration of equipment used in specimen testing and provide guidance for corrective actions[9]. Regular EQA participation has been shown to contribute to improved performance and reproducibility[10].

When availing of EQA or PT, the repository should consider if the EQA/PT program uses available certified reference materials. The repository should plan for the level and frequency of participation in the program. The documented plan should be reviewed and updated with any changes to personnel, scope of work, equipment, processes, or site relevant to the performance being evaluated. Guidance for corrective actions as a result of participation should be followed to help achieve a satisfactory performance.

***BEST PRACTICE:*** Repositories should follow an EQA or PT program, when available and feasible including periodic (*e.g.*, once a year) evaluation of performance and accuracy of methods.

***BEST PRACTICE:*** Accuracy of assays should be trended with a QC chart to identify out-of-specification (out of trend) results. These results should be documented and investigated where appropriate.



ISBER Head Office: 1618 Station Street, Vancouver, BC, V6A 1B6, Canada
Contact Information: T: +1.604.484.5693 • F: +1.604.874.4378 • E: *bestpractices@isber.org* • *www.isber.org*

### D3.5. Quality Control Approaches

The QC process is dependent on having documented predefined criteria associated with the intended purpose or use (as determined by the repository, the end-user, or both), and reviewing specimens and associated data to ensure they meet those criteria. Such QC reviews may be undertaken at a number of stages during the life cycle of the annotated specimen and should be undertaken:

- Prior to distribution for research (to assess fitness for the intended purpose).

QC reviews can also be conducted:

- At the point of acquisition or accessioning by the repository (to verify quality).
- Regularly throughout retention period (to monitor for degradation).
- Subsequent to a deviation in storage conditions (to detect for degradation if an unplanned temperature or other deviation occurs).

QC analysis can be contracted to external organizations (*e.g.*, collaborators, professional organizations), to account for any bias inherent to the repository in both the life cycle process and in QC analysis. The repository should be aware of the quality standards or other conformity frameworks to which such organizations are certified or accredited[11].

QC may be undertaken by the receiving end-user. Any feedback (see *D3.8.3. External Feedback*) provided to the repository can further enhance the value of the specimens and data. QC involves testing specimens and data against the quality criteria using standardized and validated methods. The results should correlate with the predefined quality criteria related to the downstream analytical purpose. A series of international technical standards exists for different specimen types, *e.g.*, molecular in vitro diagnostic examinations[12] (see *D4.2. Standards*). By implementing and/or upholding a QC process, the repository is in a position to provide specimens and data that are considered fit for the intended purpose to end-users. This can help develop positive relationships with such stakeholders and encourage re-use of a repository.

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). When using external contract testing laboratories for QC testing (particularly any mandatory safety testing), the repository should ensure that the test(s) in question has/have been validated against the particular analyte(s) provided.

***BEST PRACTICE:*** A repository should identify when QC of specimens and associated data will be performed throughout the life cycle of the specimen and associated data and what criteria will be used at each stage.

The following can be considered for a QC process:

- Establishment of measures to be used to assess quality: For QC procedures to be effective, a repository needs to understand and justify the quality criteria that help to demonstrate FFP (see *D1. General Introduction to Quality Management*). Documentation supporting the establishment of quality criteria based on the intended purpose should be retained for future reference. This can help develop realistic priorities when making specimens and data-handling process improvements.
- Sufficiency of resources: QC analysis, QC reporting including non-conformities and any appropriate responses (see *D3.8. Quality Improvement*) should be sufficiently resourced.
- Generation of useful insights: Data corresponding to relevant information can be documented and reviewed periodically to determine performance trends of processes over time. Gathering data provides insights to the effectiveness of a QC process plan, which can be used to adjust process workflows, give feedback to the QA process, and find ways to improve. Such information may include:
    - Percentage of specimens and data that meet quality expectations.
    - Average end-user satisfaction scores.
    - Level of variation in the specimens and data specifications.
- Double checking of critical QC elements (*e.g.*, bar coding, data transfer, supervisory review of records, batch record review): Confirmation is important to enhance accuracy and to reduce the likelihood of operational mistakes.
- Decision-making system: For specimens and data that do not meet pre-identified QC criteria, a system should be in place to either withdraw these from distribution or provide to the end-user, reporting the QC results. This should be performed in consultation with the end-user.

Many QC processes are standard across all repositories and 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 specified limits when stored under defined conditions.
- Consent: For human specimens and data, specimen type and use are consistent with the level of consent provided by the participant.

The QC process for living specimens can be more complex and costly. Examples might be soil specimens with living microbes, primary cancer cells in liquid nitrogen ($LN_2$) or human tissue for surgical transplantation. In depth QC testing for living specimens can help to rate the usability and underscore a level of confidence to the end-user that the specimens are fit for purpose. During life cycle stages, there are many opportunities to alter the health and functions of the cells.

***BEST PRACTICE:*** A repository should create a quality control document (*e.g.*, certificate of analysis, report) for critical specimens and associated data for provision to stakeholders such as end-users. Such a document can help to demonstrate fitness for purpose.

### D3.5.1. Quality Control for Solid Tissue Specimens

QC examination of solid tissue specimens (*i.e.*, remnant clinical tissue from surgery, autopsy, or cytology regarded as excess to diagnostic needs) should be appropriate to the intended use. Referencing a related diagnostic pathology report alone is insufficient for the purpose of QC of such specimens. Due to tissue heterogeneity, QC for tissue specimens should be aliquot-specific with percentages of tumor, normal, necrosis, and/or fibrosis recorded during an examination by a pathologist or an equivalently competent individual. This verification should be performed by microscopy on a representative section (*e.g.*, 3-5 micrometers) from each tissue block.

This may be accomplished through hematoxylin and eosin (H&E) top-slide creation from FFPE and/or optimal cutting temperature compound (OCT)-embedded tissues. Less resource-intensive alternatives taking advantage of mirror-faces of tissue specimens have been described. 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[13]. See *D4.3. Multipurpose Quality Management Resources* for pathological-related guidelines.

***BEST PRACTICE:*** The histological composition and pathological changes should be verified for all tissues collected. This involves having a pathologist or an equivalently competent individual verify that the tissue is representative of the participant/donor diagnosis and has the specific features that are important for analysis (e.g., cellularity, presence/extent of necrosis).

***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 quality management.

### D3.5.2. Quality Control for Fluid Specimens

In some situations, fluid specimens may require assessment as to their integrity in view of the detection or measurement of specific analytes. The Centers for Disease Control (CDC) provides a Quick-Reference Tool for Hemolysis Status[14]. Molecular markers to assess specific preanalytical variables can be used, such as the hemoglobin content to assess serum/plasma hemolysis or the sCD40L content to assess serum exposure to room temperature[15]. Taurine is useful as a serum specific quality indicator for time-to-centrifugation. In many instances, quality control can only be performed in reference specimens and in a targeted manner once the end-use analysis is known[16,17].

### D3.5.3. Quality Control for Cells, Viability, and Vitality

Contamination control methods should 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. There are levels of testing to enable the determination of both viability and vitality of living cells.

Viability is an objective measure of the number or ratio of cells that have survived out of their original endogenous environment after collection/acquisition, processing, storage, or distribution. An international standard exists for testing and characterization of cellular and therapeutic products[18]. Viability assays (also known as live/dead assays) may specifically label or identify live cells, dead cells, or both.

Differentiation testing of live versus dead cells is generally based on cellular membrane integrity (*e.g.*, dye exclusion such as trypan blue or fluorescein diacetate) or metabolic/enzyme activity (*e.g.*, Calcein AM dyes cleaved by


ISBER Head Office: 1618 Station Street, Vancouver, BC, V6A 1B6, Canada
Contact Information: T: +1.604.484.5693 • F: +1.604.874.4378 • E: *bestpractices@isber.org* • *www.isber.org*

intracellular esterases). Such assays should be standardized and validated prior to use. Viability testing does not usually address the health or fitness status of the living cells, nor predict how long they might survive. Researchers often require cells or tissues to function in a similar fashion as they would in their native roles. In these cases, a measure of vitality is crucial.

Vitality is the assessment of the fitness or health of the cells/tissues. As each cell type or tissue system performs unique functions, the selection of key fitness indicators and tests to measure is subjective and can be challenging. The following list of vitality tests reflect increasing comprehensiveness and complexity of health and fitness examination:

- Programmed cell death (apoptosis) assays show cells that are dead and/or those that will soon die by detecting the series of molecular changes that precede cell death. These assays cross over between both viability and vitality and include assays such as terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assays to detect DNA fragmentation or caspase activation assays.
- Cell growth and/or division assays offer the next level of fitness testing, as cells need to be relatively healthy over a longer period to survive and proliferate. While these generally do not require specialized kits and reagents, cells must be brought out of stasis and into conditions amenable for growth.
- Cell function assays can represent the most challenges, as the function under investigation should be aligned with the particular cell type but are the most informative as they further report on the fitness of the cells. The wide range of assays can include detection of secreted compounds to the presence of specific proteins to responses to antagonistic agents. End-users should be consulted as to what parameters of cell functions are important for their intended use. There are general functional tests that can be applied to most cells, including transepithelial electrical resistance (TEER) measurement[19,20].

### D3.5.4. Quality Control for Microorganisms

Characterization assesses different types of quality features distinctive to microorganisms (and protists). Characterization methods include:

- Morphological: focuses on physical appearance, *e.g.*, size, shape, color, and other features. Single colony streaking on agar plates (with or without chromogenic indicators) and observation of colony size and morphology can be used for microbial macroscopic assessment.
- Phenotypic: focuses on observable traits and behaviors, *e.g.*, growth patterns, nutrient requirements, enzymatic activities, and antibiotic resistance profiles. Phenotypic characterization includes both macroscopic and microscopic morphology assessment. Various microscopic techniques such as hanging drop, wet mount, or fixed stained slides (*e.g.*, gram stained to differentiate bacteria into gram-positive and gram-negative based on the physical properties of their cell walls) can aid determination of purity, viability, or identity of the culture.
- Genetic/Genomic: focuses on genetic composition; variation or relationship to other strains, at the genetic or market level; and can help determine potential virulence factors. Analysis can be molecular in nature (*e.g.*, DNA sequencing, genotyping specific markers, polymerase chain reaction [PCR]-based profiling, microarrays, ribotyping). Genotypic characterization can reveal insights into the specific genetic variants a microorganism possesses and their potential functional or phenotypic consequences.
- Biochemical: focuses on metabolic pathways including substrate use patterns, and production of specific metabolites, proteins or enzymes, and peptides (*e.g.*, matrix-assisted laser desorption/ionization - time of flight [MALDI-TOF]).
- Serological: focuses on antigenic properties and immune response, particularly for pathogenic strains.
- Ecological: focuses on ecological niche, habitat preferences, and interactions within the natural environment.

A combination of different characterization methods can be applied for taxonomic determination and identification purposes. Functional assays include viability assays or assays for cytopathic effects, antimicrobial resistance, biochemical stability, phenotyping, and plasmid stability. The choice of methods to be deployed depends on the specific microorganism, available resources, and the criteria for specimen and data application.

Reference strains can also be used to authenticate microorganisms. Where possible, such reference strains should have a known and documented identity, preferably obtained from reputable culture collections or microbial resource centers. To help to evaluate consistency of deposited microbial specimens, it is good practice to make preparations of microorganisms (*e.g.*, microbial slides or dried cultures that highlight the strain's characteristics) upon reception. Prior to distribution, a strain can then be compared for conformity to that originally deposited. To further aid identification and recognition, preparation of visual references (*e.g.*, drawings or captured images, see *D3.5.7. QC for Digital Imaging*) is also recommended, where appropriate.

Contamination control methods for bacteria and yeast/fungi can be applied to cultures prior to distribution, at accession or in the process of regeneration of depleted cultures, by use of selective antibiotics to eliminate microbial contamination. Quality control for purity can be performed on single species specimens. However, certain cultures need to be maintained in a non-axenic state (*i.e.*, in association with another species, variety, or strain), *e.g.*, obligate plant pathogens and assemblages of microorganisms, symbiotic and beneficial associates found in microalgae and cyanobacteria collections.

### D3.5.5. Quality Control for Plant Specimens

The QC process of plant repositories (*i.e.*, gene banks, culture collections, germplasm repositories, seed and field banks) ideally involves both[21]:

- Germplasm characterization before and after storage and at the point of distribution.
- Plant health (phytosanitary) checks, safety duplication, and passport documentation with assignment of an accession number.

Plant specific vouchers (*i.e.*, taxonomy generally based on morphological and/or genetic divergence properties) can assist. Seed germination testing prior to storage can help to assess seed quality, if a sufficient seed quantity is available (accession sizes are often smaller for wild species) and germination conditions are optimized. In the case of seed for crop and agricultural use, the International Seed Testing Association develops and publishes internationally approved rules and standard procedures for uniformity in seed testing worldwide[22].

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), and confirmation using molecular markers.

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.

### D3.5.6. Quality Control for Nucleic Acids

Preparations of nucleic acids may include double-stranded DNA, single-stranded DNA, single-stranded RNA, oligo, and free nucleotides, to various extents. DNA and RNA quality entails concentration, purity, and integrity measurements. Nucleic acid extraction protocol must include DNase or RNase steps to eliminate genomic DNA from RNA preparations and RNA from genomic DNA preparation, respectively[23]. Agarose gel electrophoresis (in combination with ethidium bromide staining) is used to estimate the concentration and intactness of the nucleic acid by direct visual comparison to molecular weight markers of known size and concentration[24]. Spectrophotometry can be used to estimate DNA or RNA concentration and to analyze the purity of the preparation[25]. Typical wavelengths for measurement are 260 nm and 280 nm. Absorbance ratios (A260/A280 ratios and A260/A230) are used as a measure of nucleic acid purity. A260/A280 ratios of ~1.8 and ~2.0 are generally accepted as indicators for pure DNA and RNA, respectively. Strong absorbance at 230 nm is indicative of organic and salt-based impurities. Fluorescence-based methods are more sensitive than absorbance, particularly for low-concentration samples, and the use of dsDNA- and RNA-binding dyes allows more specific measurement of nucleic acids[26]. RNA integrity number (RIN) is used to evaluate the suitability of RNA for gene expression studies. A RIN of 10 is indicative of the best quality RNA whereas lower values result from RNA degradation. Similarly, DNA Integrity Number (DIN) is a numerical assessment of DNA integrity.

DNA identity can be established upon receipt or extraction by fingerprinting using multi-locus single nucleotide polymorphism (SNP) or short tandem repeats (STR) genotyping. DNA fingerprinting can identify any potential mishandling of specimens from collection or acquisition through to distribution, disposal, or transfer.

Personnel may need to be cognizant of the possibilities of multiple species representation within nucleic acid specimens (*e.g.*, in environmental or contaminated specimens) and can consider assessment for the presence of bacterial/fungal/human genomic DNA by using species specific DNA primers/PCR. DNA barcoding using a short section of DNA from specific gene(s) and comparing with a reference library of such DNA sequences can enable unique identification of part of an organism to a species[27-30].



ISBER Head Office: 1618 Station Street, Vancouver, BC, V6A 1B6, Canada
Contact Information: T: +1.604.484.5693 • F: +1.604.874.4378 • E: *bestpractices@isber.org* • *www.isber.org*

### D3.5.7. Quality Control for Digital Imaging

Imaging of biological and environment specimens is used for a wide variety of repository functions, from archiving specimens to obtaining data associated with the specimens. While the traditional method of direct or live viewing (*e.g.*, personal observation of histology slides through a microscope) may be important in repository operations, digital or digitized images enable image storage and/or expanded image analysis. Digital images are suitable for local and remote web-based individual and concurrent multi-viewer access), and analysis can include annotation of regions of interest, assessment, and interpretation, followed by archiving. Personnel should be specifically trained and deemed competent (see *Section E. Training and Competency*) in imaging, the equipment, and adherence to SOPs.

The repository should consider fitness for purpose of their digital images. The use of this technology facilitates rapid remote review and can avoid shipping of specimens that are deemed not fit for purpose. The image data files should be managed according to the data management plan (see *Section I2. Data Management*). For image QC, such images require significant data storage as well as sufficient upload/download capabilities; thus, the storage, backup, and transfer capacity required for a large number of such images should be considered and managed appropriately. QC considerations of acquisition of such images (and/or digitization of traditional images) and their analysis are important and are addressed below.

**Image Acquisition and/or Generation of Digital Images**

Images of specimens are acquired through the use of microcopy (*e.g.*, photomicrographs of histological sections of tissue specimens on prepared slides) as well as a variety of other techniques and technologies (*e.g.*, x-ray, infrared thermography, optical coherence tomography, and magnetic resonance imaging [MRI]). Multiple modes of imaging can also be performed on single specimens, providing a potential wealth of data and value. QC of image acquisition is critical for downstream applications, including image analysis and should include:

- Regular equipment calibration (critical parameters may include brightness, contrast, spatial resolution, and color accuracy [see *D3.6.2.2. Calibration*]) as well as maintenance of imaging equipment (see *Section H12. Equipment Maintenance, Repair and Replacement*).
- Prior to image acquisition, checking specimen preparation quality (*i.e.*, that specimen positioning is optimized, slides are dry, free of wax, etc.) (see *Section J3. Specimen Integrity*).
- The use of standardized SOPs and settings for consistency across imaging sessions and devices. Factors to consider include image acquisition parameters (*e.g.*, positioning, exposure time, field of view, slice thickness, signal-to-noise ratio, image resolution), image quality, reduction of artifacts, and image processing or analytical techniques.
- Comparisons with reference digital images or previous datasets where deemed useful.

**Analysis of Digital Images**

Digital image analysis is the process of extracting or obtaining meaningful data from digital images. Analysis ranges from counting cells on a histology slide to using artificial intelligence-assisted, multifactorial analysis. Understanding the platforms, technology and processes can help to highlight the particular analytical parameters required (*e.g.*, what parameters a program uses to perform automated cell counts) in order to develop an effective QC approach.

QC considerations for image analysis should include:

- Prior to analysis, QC checks to verify the effectiveness of any image processing steps, *e.g.*, image registration, noise reduction, normalization, and intensity correction.
- During image analysis, QC metrics include specimen segmentation accuracy and feature extraction consistency.
- Where multiple observers conduct image analysis (including any algorithms used), QC measures can be used to compare the results.

As a different application of digital imaging, the results and conclusions of digital image analysis may be used as QC measures in respect to validating or confirming other information on specimens (*e.g.*, findings of cancerous cells in a biopsy specimen from a suspected cancer diagnosis)[31].

**Digital Pathology**

Traditionally, digital pathology is a formal discipline of image analysis that focuses on information generated from digitized specimen slides, incorporating image analysis with goals of phenotyping, ascertaining disease state and

type, and/or validating other medical or scientific information and making clinical diagnoses. In the broader sense, this may be expanded beyond microscopy images and include images generated by other technologies and platforms. Digital pathology is integrated with other electronic applications such as inventory management systems, electronic medical records, medical imaging, molecular testing systems, and specimen inventory management systems (see *Section I. Information Management* and *Section J8. Specimen Inventory Management*). Digital pathology facilitates complex image analysis of both morphology and tissue-based assays (*i.e.*, immunohistochemistry).

For collection of excess tissue after human surgical resection, verification of the diagnosis and percentages of tumor and necrosis should be performed by a pathologist for each aliquot to account for tissue heterogeneity, *e.g.*, top-slide analysis for embedded aliquots or mirror-slide analysis to permit snap-freezing. It can aid in assessing tissue quality by detecting and measuring features such as percentage tumor, stroma, necrosis, cellularity, and other morphologic features. Such approaches require validation prior to implementation (see *D3.6. Validation, Verification, and Quantification*).

Detection of artifacts and defects introduced during slide preparation and image acquisition for digital pathology is recommended to determine any images that might need to be reproduced, but can be challenging to perform manually. This QC step can be automated in order to determine any areas that should be avoided during analysis[32]. One of the most important elements to consider for QC in digital pathology is the variation that ensues from inter-user analysis. Expertise should be identified for consultation purposes and organizational or repository strategies for achieving consensus should be followed. Overall, QC should encompass the aforementioned aspects of image acquisition/digitization of images; process, equipment, and technology validation; and data management, including data integrity, interoperability, portability, and reconciliation (see *Section I3.7. Interoperability, Portability, and Reconciliation*). The European Society of Digital and Integrative Pathology has produced a set of recommendations for implementation of a Digital pathology workflow including appropriate quality control to guarantee the safety of the process[33].

## D3.6. Validation, Verification, and Qualification

Validation, verification, and qualification are separate but complementary activities that are used to ensure the quality and integrity of a process. The understanding of these terms often differs with various factors, such as regulations, organization, domain, industry, stakeholders, and the associated requirements. A repository should determine what these requirements are prior to establishing evaluation procedures along the lines of qualification, validation, and verification.

A repository should ensure that any process used in the specimen or data life cycle that can impact fitness for purpose has been evaluated based on performance characteristics and/or data from validated analytical tests in advance of implementation. Within the process, for components already validated by the manufacturer or within published literature, the repository only needs to verify that the specific requirements for their intended purposes are met. Components of any process may include but are not limited to:

- Reagents and consumables (*e.g.*, collection containers, pipette tips, commercial kits such as biomarker detection assays, culture media) (see *D3.6.1. Reagents and Consumables*).
- Specimen identifiers and labels (see *Section J3.1. Identification of Specimens*).
- Storage equipment (*e.g.*, freezers, refrigerators, environmentally controlled units) and instruments (*e.g.*, centrifuges, liquid handling units, measuring instruments) (see *D3.6.2. Instruments and Equipment*).
- Data storage and software systems (see *Section I. Information Management*).
- Any protocol or method that could affect data or specimen quality (*e.g.*, aliquoting specimens, scanning of container labels).

Validation is documented confirmation that a process consistently produces a result that meets the specifications of its intended purpose. This includes evaluating the design, performance, robustness, stability, and reproducibility against a set of established criteria (*e.g.*, performance specifications) relating to that purpose. These criteria may be established by the manufacturer, repository, end-user, or other, *e.g.*, regulatory agency.

Validation is typically undertaken within a repository for a new or existing modified process that does not already have pre-established performance characteristics related to the defined purpose. Examples of modification might include change of location, specimen type, protocol, reagent supplier, and repair or replacement of equipment involved in the process. If undertaking validation, compiling a documented validation plan will help to determine what should be addressed. A validation plan helps to determine what will be included during validation (*i.e.*, scope), the acceptance criteria (*e.g.*, for performance), any specific conditions, and assess for various traits such as specificity, accuracy, and robustness.



ISBER Head Office: 1618 Station Street, Vancouver, BC, V6A 1B6, Canada
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See ISO 21899, General requirements for the validation and verification of processing methods for biological material in biobanks[34]. Examples of validation can be found within the literature[35,36]. Additionally, validation may also include ongoing monitoring and testing of the process to ensure that it continues to meet the specified requirements and to identify any potential issues early on.

Verification refers to the periodic evaluation (*e.g.*, testing, simulation) and confirmation that the process meets the specific requirements and expectation of the intended purpose in a specific setting. Verification is a less extensive undertaking than validation. Repositories may choose to verify an established process that already has documented performance characteristics pertaining to the purpose for which it is intended to be used. Verification checks that the adopted validated process works as intended and produces accurate and precise results within the repository's specific context, considering the conditions, personnel, and in interactions with existing systems.

Qualification is evaluation of an instrument, equipment, or system, often as part of validating/verifying a process to ensure suitability for the intended purpose (see *D3.6.2. Instruments and Equipment*). Qualification activities may include inspections, testing, and demonstrations. The goal is to provide documented evidence and confidence that the instrument, equipment, or system has been designed and installed correctly, and that it is operated and maintained to reliably support the intended purpose in a given environment. Examples include: qualifying a controlled rate freezer as part of validating a cryopreservation process and qualifying an autoclave as part of validating a sterilization process.

The goal of validation, verification, and qualification is to ensure that the biobank's infrastructure and processes meet the necessary standards for the reliable management of specimens and data life cycle.

All documentation related to testing and results should be maintained and made available for audits (see *Section D3.7. Auditing for Performance Review*) and kept for future reference or compliance with any regulatory or other requirements[11]. Additional documentation includes contact information for key personnel, user/service manuals, calibration certificates, maintenance logs, and any factory/manufacturer acceptance documentation. All documentation should be securely stored in a known and restricted location available to personnel; see *D3.2.2. Storage and Retention of Documented Information*.

### D3.6.1. Reagents and Consumables

Any reagent or consumable used in the repository should have been validated by the manufacturer to confirm it is suitable for its intended use and meets the necessary performance specifications. The repository should verify that validated reagents and consumables perform as intended. When possible, lot-to-lot testing is an important step to verify each lot of reagent or consumable is consistent with previous lots. This verification can help prevent introducing a preanalytical variable into the specimen collection that could confound later results.

### D3.6.2. Instruments and Equipment

The installation and operation of instruments and equipment should be evaluated prior to use per manufacturer recommendations and as determined to be fit-for-purpose with repository practices. This includes ensuring correct installation, and setup should be verified and documented using manufacturer recommendations with respect to infrastructure and facility resources (access, space, electrical power, $LN_2$ supply, etc.). Other important activities for instruments and equipment should include calibration and temperature mapping, where relevant.

#### D3.6.2.1. Installation, Setup, and Qualification

Installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ) are independent and documented procedures used in tandem to verify and test that instruments and/or equipment are installed correctly, work well, and perform as required. IQ, OQ, and PQ are all performed against a written design/functional specification that sets out the requirements that need to be met including appropriate tolerance limits.

- IQ oversees and verifies every physical aspect of the instrument or equipment (materials, dimensions, pressure ratings, etc.) and components (operational parameters, accuracy, voltage, etc.).
- OQ is testing of each individual component/feature/physical specification of the equipment.
- PQ, much like OQ, tests the operational requirements of the equipment but under the real-world settings and conditions that the equipment would be subject to during use[37,38].

Some countries require certification of all equipment under pressure (*e.g.*, $LN_2$ supply equipment) by a special governmental body or agency. A repository should determine that the equipment used meets relevant regulatory and legislated requirements for health and safety. The performance of all previously-validated/qualified equipment and related software should be re-qualified prior to use following repairs that affect the instrument's operating capabilities, as per manufacturer and/or organizational recommendations.

### D3.6.2.2. Calibration

Any device that provides analog or digital measurements is considered an instrument and requires calibration. Calibration is the process of comparing the output or indication on a device (*e.g.*, measurement instrument) with a value traceable to an applied standard (often a national or manufacturer standard), within a specified accuracy. Calibration may indicate where adjustment to the instrument is necessary to ensure that the output or indication agrees with the applied standard. A system for calibration should be in place and address each uniquely identified item to be calibrated. At the time of installation, instruments should be factory calibrated with documentation provided or may require verification and/or calibration.

Instruments can include sensors (*e.g.*, temperature and $LN_2$ level) as well as any secondary systems (*e.g.*, for remote monitoring and alert). The repository personnel should determine calibration frequency according to manufacturer recommendations, impact of instrument failure, requirements for specificity, and performance history of the instrument. Critical safety devices, *e.g.*, gas sensors, may need to be calibrated at a more frequent interval depending on the potential outcome of device failure. Personnel performing calibration should be deemed competent to do so.

***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 SOP used to perform the calibration.

***BEST PRACTICE:*** Repositories should review calibration/verification records that are provided to them from external calibration companies to assess for any issues and to authorize the process.

***BEST PRACTICE:*** Instruments used for calibrations should be verified against an approved, recognized calibrator source (*e.g.*, NIST: National Institute of Standards and Technology, USA; JISC: Japanese Industrial Standards Committee, Japan).

### D3.6.2.3. Temperature Verification and Mapping

Verification of instruments and storage equipment should be performed by the user using an independent, calibrated, secondary sensor to verify the temperature at a specified location within storage equipment (typically at the highest level at which specimens will be stored in $LN_2$ vapor storage equipment and at the door for mechanical freezers).

Temperature mapping is the process of recording the differences and changes in temperature that occur due to varying influences (*e.g.,* inventory organization, door opening, proximity to cooling fans, personnel movement, and the quantity of stored materials) at a given time. It can be used to qualify new controlled temperature environments (including storage equipment), and to provide ongoing quality assurance. It should be performed at defined intervals, and again after servicing and repair. It should be considered for mechanical freezers, freezer rooms, cold rooms (*e.g.*, walk-in environmental storage systems); $LN_2$ storage and transport equipment; incubators; and other temperature-controlled storage areas[39]. This includes areas and equipment used for the storage of components (*e.g.*, media) used in processing the specimens.

Testing intervals should be based on risk assessment of the intended use of the stored materials and patterns of unit use. Temperature mapping entails:

- Locating the points of greatest temperature fluctuation and differentials through the use of calibrated temperature sensors.
- Analyzing the causes of fluctuations and differentials.
- Determining worst case conditions, and setting upper limits on the causes for temperature fluctuations (*e.g.*, the maximum time for doors or lids of mechanical freezers or $LN_2$ storage equipment to remain open).
- Reporting results and implementing any remedial and other actions identified in the mapping report.
- Verifying the effectiveness of any remedial actions.

Locations of the sensors should be documented in the report. Sensors should be positioned to provide an air temperature reading rather than that of walls or shelves. This process helps 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.


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In liquid nitrogen ($LN_2$) vapor storage equipment, the highest level at which specimens are stored typically experiences the warmest temperatures (see *Section H2.2. Monitoring Liquid Nitrogen Storage Parameters*). For mechanical freezers, this can be at the front of upright freezers and at the top of chest freezers. A repository should determine how many sensors to use to truly reflect the actual temperature map for the storage equipment. The temperature mapping process should address specimen integrity where temporary movement of inventoried specimens is necessary to accommodate the placement of sensors (see *Section J3.5. Specimen Temperature*). Regular temperature mapping helps to ensure that specimens are stored within the specified temperature range(s).

$LN_2$ storage equipment temperature mapping is typically performed by the manufacturer or supplier as part of design qualification. Verification should be performed by the user. Some repositories may require temperature mapping to be performed on-site by the service provider before a unit is put into service, which may take 2-4 weeks depending on repository requirements.

Walk-in environmental storage systems, like storage vessels, should be temperature mapped, at time of installation, after any modifications to the space, and periodically, *e.g.,* every three years[40].

***BEST PRACTICE:*** All controlled temperature storage areas and equipment should be qualified prior to use by temperature mapping with multiple temperature readings taken throughout the storage area or unit. This initial temperature mapping should document and set operational parameters for the temperature distribution within the storage area so that warm and cold spots that could be problematic for specimen storage can be identified.

***BEST PRACTICE:*** The repository should assess and document the ongoing requirements for temperature mapping of storage areas and equipment. Where deemed critical to fitness-for-purpose, the repository should ensure that temperature mapping is periodically used to verify continued operation, where practicable.

***BEST PRACTICE:*** Processes should be re-validated when any changes are made to the software and/or automation equipment.

### D3.6.3. Preanalytical Variation

Where relevant scientific literature relating to process evaluation is lacking, the repository can undertake specimen analysis, *e.g.*, sequencing (either in-house or externally) to assess the potential impact of the most important preanalytical variables. Different specimen quality parameters can be affected by the specific procedures followed during specimen life cycle, *e.g.*, protein structure, enzyme function, metabolite levels, gene expression, DNA methylation status, cell viability, and microorganism viability.

Preanalytical variations may arise *in vivo* (generally pre-acquisition or pre-collection) and *in vitro* (primarily during collection or post collection). Examples of such preanalytical variables may include:

- Participant/donor's condition, *e.g.*, certain conditions and treatments, lifestyle factors, age, and gender.
- Timing and procedure of collection, *e.g.*, many organisms exhibit biological rhythms. Timing of collection may impact on analysis of such factors.
- Organism's environmental niche/type of habitat, host, axenic or in combination with other organism(s), season of collection, and microbial phase variation, warm and cold ischemia times for solid tissues.
- Type of collection tube and cryopreservation container, culture medium composition, pre-centrifugation time and temperature, centrifugation speed, temperature per cycle, and number of centrifugation cycles.
- Number of freeze-thaw events, type, and duration of fixation.
- Time delay before placing in long-term storage, temperature of long-term storage.
- Protocol of cryopreservation including instrument, cooling rate, and reagents used, warming rate.

Preanalytical variations should be noted and documented whenever possible and appropriate as an important component of quality management, see *Section I3.8. Data Standards* for information on SPREC (Standard PREanalytical Code). Preanalytical variations extend beyond the choice of methods and emphasize the importance of standardized protocols, quality control measures, and appropriate specimen and data management techniques. By addressing these variables effectively, repositories can take measures to minimize variations, where practicable, to ensure accurate, reliable, and reproducible results in downstream analyses.

Repositories should implement a system to track QA variables and generate reports relating to critical specimen-handling management that allow for aggregation of preanalytical data. This system should be evaluated (see *Section I3.11. Validation of Inventory Systems* and *D3.7.1. Internal Audit*).

***BEST PRACTICES:*** Sources of preanalytical variation with potential impact on fitness for purpose should be documented, and, where practicable, controlled. End-users should be provided with the recorded preanalytical variables so that informed, evidence-based assumptions and conclusions about the experimental data can be made.

***BEST PRACTICES:*** A pre-approved document should be established which describes the methods used in verification/validation/qualification, what is in or out of scope, and the proposed criteria to be used to determine the outcome of the evaluation. Details including results should be documented in a report post evaluation.

## D3.7. Auditing for Performance Review

Audits are tools that can be used in different forms to help a repository produce the evidence to determine that it is doing what is expected of it by stakeholders.

Auditing is a formal, planned, and documented process. It involves obtaining relevant information (evidence) and evaluating it to determine the extent to which specified requirements are fulfilled. Data relating to documented practices for auditor assessment may be generated from within the inventory management system (see *Section I3.11. Validation of IMS*). The auditor's report (see *D3.7.3. Audit Reporting*) sets out the opinion of the auditor concluding with the extent of fulfillment and any follow-up actions that were deemed necessary (*e.g.*, evaluating effectiveness of corrective actions). Some repositories are required by internal or external stakeholders to follow compliance frameworks and are obliged to undergo external auditing to determine whether the repository continuously meets the compliance requirements.

Conformity assessment is the demonstration that specified requirements (conformities) are fulfilled. The repository is subject to self-assessments and/or external assessments, such as by external users, certification/accreditation bodies, and regulatory agencies, as appropriate. Regulatory agencies that access conformity in repositories vary by local, national, or international regulations.

The process of conformity assessment can have negative outcomes, *i.e.*, demonstrating that the specified requirements are not fulfilled (non-conformities). There are three types of conformity assessment that can be applied to a repository:

- First-party conformity assessment: When a repository assesses its own conformity to specified requirements internally (*e.g.*, internal audits).
- Second-party conformity assessment: When a repository has its conformity to specified requirements assessed by a stakeholder (*e.g.*, supplier, end-user, funder).
- Third-party conformity assessment: When a repository has its conformity to specified requirements assessed by an independent party that has no interests in the repository's outcomes (*e.g.*, certification, accreditation).

Audits should be undertaken on a regular basis (*e.g.*, quarterly, semi-annual, or annual), covering all QM documentation, operation, and processes, including technological processes (see *Section I3.6. Audit Trail and Traceability*) and inventory systems (see *Section I3.1. Specimen Location*). Audits should be performed and primarily directed at prevention of non-conformities as well as detection of the need for corrective actions and process improvement opportunities. Audits may also be part of a corrective/preventive actions (CAPA) plan in response to an 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.

### D3.7.1. Internal Audit

Internal audits (also referred to as first-party conformity assessment) are self-assessments by which a designated individual familiar with the specific work being assessed but not directly involved in that work should be responsible for the assessment activities. For this role, the individual should be someone who is not directly supervised by Repository Management and should report to a separate department or division (*e.g.*, responsible for quality assurance). For small repositories with limited personnel, possible options can include:

- An internal audit performed by non-repository personnel from within the parent organization. Such personnel should have an understanding of quality and/or the repository output, as well as auditing).
- Contracting an auditor from an external provider.
- Adopt a number of approaches, such as the repository management performing a critical audit, participation in quality assessment schemes such as ISBER's Biobank Assessment tool (BAT)[41] (see *D4.3. Multipurpose Quality Management Resources*), and/or other strategies.

Where repository personnel directly conduct internal audits, the auditors should not assess their own areas of responsibility and the repository should assess the risks, such as lack of expertise or oversight authority as well as risks to impartiality, *e.g.*, collusion with co-worker process owners to present favorable observations.


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The repository should plan, implement, and maintain an internal audit procedure (the audit plan) to ensure compliance with regulatory, technical, end-user, or any other relevant quality requirements. The repository should define the frequency of internal audits balancing quality needs and resources needed to execute audits.

The audit plan describes the audit objectives and scope, the entity and/or the sites being audited, the audit team, responsibilities for areas under audit, schedule, audit criteria, methods to be used, etc. In addition, the roles and responsibilities to manage the audit plan should be described. The audit plan should be disclosed to Repository Management prior to the audit.

The audit scope describes what will be audited and should be consistent with the audit schedule. The audit schedule is a breakdown of what processes get audited when and by which auditor, by day and time. The audit criteria are the benchmarks against which compliance is determined, such as procedures, guidelines, standards, norms, codes, regulations, etc.

***BEST PRACTICE:*** The repository should have a procedure for internal audit, including periodic verification of the specimen inventory (see *Section J8. Specimen Inventory Management* ), associated data, and any database or IMS (see *Sections I2. Data Management* and *I3. Inventory Management Systems*).

### D3.7.2. External Audit

External audit is an analysis performed by a suitably qualified independent auditor who is not associated with the repository. External audit is an important element of quality management. External audits can also be referred to as second-party or third-party conformity assessment depending on the auditor's qualifications as well as their relationship with the auditee.

Second-party conformity assessments are commonly performed by stakeholders, such as end-users of specimens and/or data, users of services provided by the repository, funding entities, or suppliers of specialist materials.

Third-party conformity assessments are conducted by independent organizations authorized to formally recognize compliance with normative references, such as certification and accreditation bodies.

Certification of repositories is documented confirmation through third-party assessment that a repository's system or product is in compliance with a set of requirements. Certification can provide a level of assurance of system or product performance. For example, a repository can have a certificate issued by an authorized certification body attesting compliance to specific quality management system requirements (*e.g.*, ISO 9001[1]).

Accreditation of repositories is an attestation conveying formal demonstration through third-party assessment of a repository's technical competence. It provides additional assurance over certification by recognizing that personnel are deemed competent. For example, a repository can be formally recognized by an authorized accreditation body as technically competent and impartial, and that it operates consistently when performing tests; producing reference materials; or when receiving, preserving, and distributing specimens and data (*e.g.*, ISO 20387[42], Biorepository Accreditation Program from the College of American Pathologists - CAP BAP[43]).

### D3.7.3. What to Expect from an Audit Report

Following an audit, the auditing team should deliver a report of the results of the audit. Audit reports typically contain the following information:

- List of auditors and those being audited (position/function/department).
- Period of audit (start and end dates).
- Audit objective, scope, and criteria.
- Audit findings and conclusions (description and evidence of compliance or non-compliance, including reference to the relevant benchmark criteria, *i.e.*, norms/standards/procedures/instructions).
- Auditor(s) signature.

The repository should implement corrective and preventative actions against non-conformities and risks identified during the audit (see *D3.8.1. Non-Conformities*, *D3.8.2. Corrective and Preventive Actions*).

## D3.8. Quality Improvement

### D3.8.1. Non-Conformities

A process for documenting non-conformities (i.e., deviations from established policies and procedures or defects) 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.

### D3.8.2. Corrective and Preventive Actions

The CAPA (Corrective and Preventative Action) process is centered on the development, implementation, and documentation of actions to correct an incident when it has already occurred (corrective action) or to avoid occurrence of an incident (preventive action). These actions help leadership determine and implement the appropriate response to correct the initial undesirable situation.

***BEST PRACTICE:*** Repositories should utilize quality indicators as a way to measure the effectiveness of the quality assurance program and have plans to address deficiencies that may arise.

### D3.8.3. External feedback

Eliciting the voice of the end-user can be beneficial for the repository, as end-users are well-positioned to highlight any gaps in their experience. For repositories willing to engage with the process, innovative ideas from external parties to the repository can encourage continual improvement through forward thinking. In this way, feedback is considered a component of quality management. Potential benefits include retention and expansion of a repository user network through effective impact on end-user success. Feedback from end-users is distinct from external audits. Communication practices are further detailed in *Section A5. Communication and Repository Promotion*.

A repository can prepare for feedback using the following steps.

- Defining objectives for feedback:
  - Identifying what needs improvement.
  - Understand if the repository organization is willing to support resulting improvements.
- Identifying the key relevant parties and roles:
  - Instigator or process owner, *e.g.*, repository Director, or other.
  - Process team, *e.g.*, delegated authority such as Quality Manager, analysis team.
  - Feedback providers, *e.g.*, end-user(s), researcher(s), collaborator(s).
  - Other interested parties, *e.g.*, end-users not directly involved in the feedback process.
- Developing feedback mechanisms, such as:
  - Delivery and collection tools and platforms to host interactions such as surveys, discussion/focus groups, interviews.
  - Fulfilling any ethical obligations, *e.g.*, informed consent if not anonymous.
  - Data analysis tools and capabilities.
  - Reporting tools.
- Implementing a feedback loop:
  - Assessing the feasibility of new ideas for improvement.
  - Implementation.
  - Monitoring for success and sustainability.
  - Communication to feedback providers in a demonstration of appreciation for their efforts and for their direct benefit.

***BEST PRACTICE:*** Repositories should create a plan to receive feedback from end-users to determine if end-user needs have been satisfied.



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#### D3.8.4. Key Performance Indicators

Repository leadership should periodically review the overall effectiveness of their quality management program. Key performance indicators (KPIs) are often used to help with this. KPIs are those indicators that focus on the aspects of repository performance that are most critical or informative for current and future success. To help determine what kind of KPIs to adopt, the repository should appraise the business plan and strategies (see *Section A3.2. Business Planning*), stakeholder expectations, and other factors that are considered critical for success. Examples include receiving and/or distributing rates, end-user satisfaction rates (as when linked to evaluation of FFP), and remediation of non-conformities rates. KPIs can be tracked over time using daily records and/or by querying data stored within the IMS (see *Section I3. Inventory Management Systems*). The KPIs should be monitored on a periodic basis to identify trends and risks (see *Section B1.3. Identification of Risks*), and to determine when actions should be taken. A repository's choice of KPIs should be reviewed over time to ensure continued alignment with the repository's purpose and business strategies.

## D4. RESOURCES FOR QUALITY MANAGEMENT

A variety of quality management tools and resources exist that repositories may consider to support their QM. Quality resource documents, such as guidelines, standards, tools, and other approaches for enhancing quality, include specialized assessment tools and personnel qualification exams and can be used either alone or in combination with others. The goal of using such resources is to enhance quality output, increase confidence, and improve reproducibility in repository practices.

The decision about which quality resource(s) to adopt is specific to each repository's goals and quality criteria. Implementation of a quality resource should strike a balance between effort and cost, but consideration should also be given to regulatory requirements (local, national, regional, *etc.*), the types of quality resources available, and the needs and demands of interested parties. In the case where repositories may want to adopt more than one resource, whether such resources are complementary without undesirable overlaps should also be taken into account.

***BEST PRACTICE:*** The repository should carefully consider the tools available for quality management and assess those chosen for potential use for alignment to repository strategies.

***BEST PRACTICE:*** The repository should critically analyze, considering risks and opportunities, the need for implementation of quality management resources in order to avoid undesirable overlaps and unnecessary waste of efforts and resources.

### D4.1. Guidelines

Guidelines are general rules, principles, recommendations, and information intended to advise a repository on all aspects of operation including establishment, management, governance operation, access use, and discontinuation. These recommendations are statements designed to help the repository make informed decisions on whether, when, and how to undertake specific actions with the aim of achieving the best possible outcome.

In general, guidelines come from entities representing one or more sectors and are voluntary resources that can be used to support repositories' quality strategies. A repository should be aware of any species domain focus and the regularity of revision within guidelines. Examples of some guidelines for repositories include:

- *ISBER Best Practices: Recommendations for Repositories:* This regularly revised document provides guidelines and presents practices for the management of biological and environmental specimens and data collections and repositories. The practices promote the availability of specimens and associated data that are considered fit for research purposes.
- IARC Handbook for Cancer Registries[44]: International Agency for Research on Cancer (IARC) is a collection of recommendations and guidelines prepared by working groups within the European Network of Cancer Registries (ENCR) and IARC. IARC Technical Publication No. 44, "Common Minimum Technical Standards and Protocols for Biobanks Dedicated to Cancer Research," combines recommendations based on validated and evidence-based guidelines for creating and maintaining biorepositories for cancer research.
- NCI Best Practices for Biospecimen Resources[45]: This National Cancer Institute (USA) document is intended to be adapted based on the mission and scientific needs of human biospecimen resources. It identifies technical, operational, ethical, legal, and policy best practices in order to ensure a level of consistency across biospecimen resources and is regularly revised.
- WFCC Guidelines[46]: World Federation for Culture Collections provides recommendations for the establishment, operation, and long-term support of microbiological and cell culture collections.

- Biodiversity and Biobanking – a Handbook on Protocols and Practices[47]: This Global Genome Biodiversity Network (GGBN)-edited handbook represents a significant resource for the broad spectrum of biodiversity and environmental biobanking fields. It focuses on a consolidation of understanding for animals, plants, fungi, lichens, protists and environmental sampling.
- OECD Best Practice Guidelines for Biological Resource Centers: A series of best practices for Biological Resource Centers (BRCs) developed in consultation with the scientific community intended to serve as a target for the quality management of service collections. Four sets of best practices are included covering general quality aspects, biosecurity-related issues, specific guidelines for microbial BRCs, and for human-derived materials BRCs[48].

One exception to the voluntary nature of guidelines is the Good Practices series (GxP), some of which are used by regulatory agencies around the world as mandatory practices, depending on the repository's activities. GxPs include preclinical (Good Laboratory Practice [GLP]), clinical (GCP), manufacturing (GMP), and distribution (GDP), among others. A repository should determine if GxPs are applicable to its nature and circumstances. Academic and other small repositories may implement GxP guidelines to instill confidence in their operations. Other repositories may wish to use some of the principles.

***BEST PRACTICE:*** The repository should adopt guidelines relevant to the types of specimens and data collections and scope of activities.

## D4.2. Standards

Standards are documents that reflect agreement among two or more parties and provide information on requirements and specifications to ensure that products and processes are fit for their intended purpose. This document most often addresses voluntary consensus standards: voluntary, in that adoption is generally not considered mandatory, and consensus, in that a balanced representation of interested parties and experts has developed a set of requirements that serves both technology and the marketplace.

It is recommended that repositories adopt appropriate standard(s) but the standard(s) chosen should suit the repository's scope and purpose, as well as provide added benefit, *e.g.*, assurance, to stakeholders. Repositories operating in certain jurisdictions and domains are expected to implement and adhere to standards by different parties (*e.g.*, as a prerequisite to obtaining ethical approval).

There are different levels of standardization. Many are tailored within organizations (local standards, *e.g.*, rules and bylaws of individual organizations), at regional or national level (regional/national, *e.g.*, French Standard NF S96-900, Clinical and Laboratory Standards Institute) or for international use (*e.g.*, The International Organization for Standardization [ISO]).

International Standardization is undertaken by an international organization which prepares and promotes standards for application on a global scale. These standards are created by consensus of specialists from industry, government, academia, non-governmental organizations, and more, delivering impartial results. ISO is a developer and publisher of international standards. ISO standards are periodically and systematically reviewed. Within the Technical Committee (TC) for Biotechnology (ISO/TC 276) working group 2, experts develop standards for biobanking. A full list of cataloged ISO/TC 276 standard products is maintained in "Standards by ISO/TC 276 Biotechnology"[49] and includes:

- ISO 20387:2018 specifies requirements for competence, impartiality, and consistent operation of biobanks including quality control requirements to ensure biological material and data collections of appropriate quality[42].
- ISO/TR 22758:2020[50] provides guidance on how to implement ISO 20387.
- ISO 21899:2020 specifies validation and verification requirements for processing of biological materials and data[34].
- ISO 24088-1:2022 specifies requirements for the biobanking of bacteria and archaea[51].
- ISO/TS 20388 specifies requirements for animal biological material[52].
- ISO/TS 23105:2021 specifies requirements for the biobanking of plant biological material for research and development[53].
- ISO 21710:2020 specifies data management and publication requirements in microbial resource centers. For additional data specific standards, see *Section I3.8. Data Standards*[54].

Other ISO documents (from different ISO/TCs) of relevance to some repositories:

- ISO 15189:202253 specifies requirements for quality and competence in medical laboratories[55].
- ISO/TS 20658:2023 specifies requirements and good practice recommendations for collection, transport, receipt and handling of samples[56].
- ISO/IEC 17025:2017 specifies general requirements for the competence, impartiality and consistent operation of laboratories[57].



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- ISO 17034:2016 specifies general requirements for quality assurance procedures for reference material producers[58].
- ISO 9001:2015 specifies requirements for a quality management system[1].
- ISO 19011:2018 provides guidance on auditing management systems[59].
- ISO 20166 Series (Parts 1, 2, 3, and 4) offers specifications for pre-examination processes for FFPE tissue. Developed by CEN/ISO TC 140, these and other potentially useful in vitro diagnostic technical standards have been published[12].

***BEST PRACTICE:*** The repository should consider, where appropriate, implementing international standard(s) to support quality management and fitness for purpose, particularly when recommended or required by relevant stakeholders (e.g., participants, end-users, funding bodies, etc.) or by its own strategies.

### D4.3. Multipurpose Quality Management Resources

Further quality management resources may also help a repository but cannot easily be categorized as those addressed in *D4.1* and *D4.2*. They represent a blend of approaches (guidelines, non-ISO standards, assessment tools, and educational tools) that can be used for diverse purposes, such as quality assurance, accreditation/certification, education, and recognition of personnel competence. Once more, the adoption of such resources depends on the repository's strategies, resources available, and scope of activities. Examples include:

- BAT (Biobank Assessment Tool)[41] developed by ISBER to self-evaluate a repository's alignment to ISBER's *Best Practices*. Based on a survey using a risk-balanced assessment score, participating repositories receive a certificate of completion with a conformity score. Aggregated data are used by ISBER to address competency gaps.
- QBRS (Qualification in Repository Science)[60] developed by ISBER and the American Society for Clinical Pathology's Board of Certification (ASCP BOC), formally recognizes professionals qualified in repository activities. Candidates meeting the requirements (educational and experience) for the qualification are eligible to complete an online examination and, if successful, gain recognition for their competence as repository professionals.
- CTRNet (Canadian Tissue Repository Network)[61] offers two quality assurance programs: Registration and Certification. Registration is aimed at researchers planning new collections of human research specimens. Certification is primarily for repositories of human research specimens. Certification involves additional steps beyond registration including assessment of documentation and completion of education training by all repository personnel.
- Pathology guidelines including:
  - The Japanese Society of Pathology has developed guidelines for handling pathological tissue specimens for genomic research[62].
  - The College of American Pathologists (CAP)[63] has a set of guidelines and consensus recommendations, Pathology and Laboratory Quality Center for Evidence-based Guidelines to help pathologists and laboratory professionals provide more effective testing with consistent, high-quality results, and expert interpretations. CAP additionally has an accreditation program (CAP BAP)[43] designed to improve the quality and consistency of biorepositories, resulting in high-quality human specimens and genetic materials that can be used to support research.

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# SECTION E: TRAINING AND COMPETENCY

## E1. GENERAL INTRODUCTION TO TRAINING AND COMPETENCY

Repository personnel should be competent to perform the tasks detailed within their position or job description (see *Section A4.2. Repository Personnel*). Orientation, education, and training are some of the resources that can be used to achieve competency. Training contributes to personnel safety and to quality in specimen and data handling. Training, combined with an evaluation of the trainee's competency, facilitates standardization of activities and effectiveness in execution, underpinning continuous improvement. A training and competency program should be designed to:

- Assess and meet learning needs of repository personnel.
- Assess personnel competencies.
- Assess training effectiveness.
- Ensure that the competencies required for repository operation are addressed.

Training should be documented and repeated on a regular basis. Specialist or complex tasks might require support from additional training resources or time away from regular responsibilities.

### E1.1. Resources for Training and Competency

Training resources should include orientation that is specific to the job and to the location(s) of work. This should include any relevant repository documentation and practices (*e.g.*, policies, procedures).

**Orientation programs** are often organization/repository specific and can include the basic training that is defined as necessary before the work commences. This training should at least include:

- Facility security and access procedures, including emergency and alarm response (*e.g.*, specimen storage, fire, flood, gas sensors, etc.).
- Workplace health and safety including handling of hazardous materials (see *Section F. Health and Safety Training*).
- Position-specific technical procedures, including handling of specimens and data.
- Data management (*e.g.*, data entry, generation, reporting, databases; see *Section I. Information Management*).
- Ethical, legal, and social implications (issues relating to regulatory requirements, privacy, and confidentiality, etc., as applicable; see *Section C. Ethical, Legal, and Social Implications*).
- Specimen and data distribution (see *Section K. Access, Distribution, Use, Transfer, and Disposal*).
- Applicable practices and/or standards implemented by the repository.

Other repository **internal or third-party training and or educational resources** may be identified as potentially useful for repository personnel, addressing topics such as:

- Biobanking, *e.g.*, Essentials of Biobanking Course[1].
- Shipping, *e.g.*, International Air Transport Association (IATA) Dangerous Goods Regulations courses[2].
- Data protection (*e.g.*, applicable regulatory-based training) and data handling, distribution, and use[3].
- Human participant research training, *e.g.*, Good clinical practice (GCP) training, Health Insurance Portability and Accountability Act (HIPAA) training[4].
- Laboratory certification, *e.g.*, American Society for Clinical Pathology (ASCP) technician training required for specific lab-based roles[5].

**Investing in knowledge training** for specialized roles can significantly improve the efficiency of operations and the following can be considered as resources for continuous professional development (CPD):

- Repository science competency assessment can be achieved through the use of third-party tools, such as the ISBER Qualification in Biorepository Science (QBRS) (see *Section D4.3. Multipurpose Quality Management Resources*).
- Academic biobanking courses, *e.g.*, education, short courses, degrees, masters resulting in a formal recognition.

Cross-training is a forward-looking approach to expand organizational competency by training personnel with complementary skills to perform additional tasks. Cross-training can be used to build a reserve of skilled team members to resolve future staffing shortfalls and also help to improve personnel engagement and collaborative efforts. Expanding an individual's competency has the added benefit of enhancing professional development for that individual.

***BEST PRACTICE:*** Repositories should cross-train personnel in a variety of procedures to alleviate personnel burn-out, reduce turnover, and to maintain coverage should personnel levels change.


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## E2. TRAINING STRUCTURE

### E2.1. Training and Competency Program

Training programs should address all the operational needs of the repository and have defined competencies that align with its purpose/mission set out in an operational plan (see *Section A4. Repository Operations*). Competencies can include knowledge, behaviors, specialized skills, or attributes relevant to particular roles (functional competencies) or relevant to working within that particular organization (core competencies). 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 equipment required and involve appropriate quality assurance and quality control practices (see *Section D3. Quality Planning*). All personnel should be trained and deemed competent before engaging in any task or procedure that has a designated training requirement.

#### E2.1.1. Assessment of Training Needs

Repositories should evaluate the need for training by first assessing training needs. This process informs how training should be developed and determines the best approach to address the identified needs. A training matrix (sometimes called a competence or skills matrix) is a tool that can help understand the competencies already available within the repository, and support gap analysis by mapping personnel actual skill sets against repository required skills. A training matrix can be used to assess repository training needs by:

- Identifying missing competencies: insight into the strengths of the repository personnel as a whole helps to highlight the areas where skills and expertise are lacking.
- Identifying personnel with knowledge or skill gaps.
- Tracking personnel development to determine what training is needed. Using the matrix can help identify training opportunities.

A training matrix can be used as a template in personnel development by helping personnel to understand what their gaps are. Knowing what skills are needed for the next level or promotion helps to create a learning path. Where a matrix is digitalized, an option could be added to enable personnel to select a skill that they would like to improve (even if they are already deemed competent for this skill). Separately, the matrix can help develop job descriptions and select the right people for the job. A well-maintained matrix usually depicts the existing skills, the required skills, and the skills that the repository or employee is missing at any point. It can be used to prioritize training needs based on legal compliance (see *Section C1.2.1. Compliance*) and/or urgency for the repository timelines. The resulting training needs can be reported, with recommendations for budgeted and scheduled training.

In some cases, training may not be the best or only solution to address deficiencies. An assessment of the situation to determine the root cause of the deficiency may inform an alternative or additional appropriate solution.

***BEST PRACTICE:*** Personnel performance should be routinely monitored to identify needs for additional training between regular training intervals. Personnel should be informed when first hired that routine monitoring of performance is a regular practice to ensure quality and is applicable to all repository personnel.

#### E2.1.2. Training Objectives

Training programs should define training objectives that support the operational goals of the repository using an appropriate method, *e.g.*, SMART (Specific, Measurable, Achievable, Relevant, Time-bound) method. External resources that provide training should be vetted prior to use to determine that training prerequisites are met. External training may take the form of education and include coursework provided by an academic or online resource and off-site equipment training. Training for some functions may be provided by departments outside of the repository, *e.g.*, maintenance personnel, equipment vendors, infection control, air transport regulatory trainers. The repository should ensure that all personnel who enter the repository follow required safety and other procedures in performing their particular tasks.

#### E2.1.3. Training Content

Training content should be both relevant and accurate. Content should be based on the needs assessment, provide all the resources required, and be aligned to professional competencies and the training task objectives. The content of text and images etc. within all training materials should be culturally appropriate for any parties addressed therein and for the trainees. When necessary, repositories should consult with a subject matter expert (SME) to confirm all information is accurate and up to date. Training content should undergo periodic review and

revision. A schedule can be established by setting dates for expiration or renewal along with a controlled document plan (see *E2.4. Frequency of Training*). When relevant, translation of content to a different language should be reviewed by a qualified reviewer to ensure that the content and presentation remain culturally appropriate.

#### E2.1.4. Training Engagement

Training should be an opportunity for personnel to engage with both the trainer and the procedure. Interactive training should be facilitated whenever possible to allow for trainee feedback on the process. Feedback opportunities are an excellent way to improve both the content of the training materials and the effectiveness of the trainer. Practice-based learning is ideal for many repository procedures. Whenever possible, repositories should provide ample opportunity to perform tasks with practice materials for a more relaxed environment to learn. Additionally, peer to peer interaction should be encouraged. All engagement activities should be inclusive of every trainee.

#### E2.1.5. Training and Training Material Accessibility

Training should be performed in a conversational style appropriate for the trainees and the content should be in a language that personnel understand. The level of training should be appropriate to the level of comprehension, use inclusive language, and avoid confusing jargon. Training materials should be of high quality with clear text and figures appropriate for printing. Training materials should be easily accessible by personnel and updated when necessary.

Personnel should be asked to review any written procedures for which they will be responsible prior to the commencement of their training. A record indicating that the employee has read the pertinent procedures should be kept in the employee's training file (see *E2.5. Training Documentation and Records*). This record should include the title of the procedure, the employee's initials, and the date when the procedure was read. A short test can be administered to assess understanding of written material before training begins.

#### E2.1.6. Training Evaluation

Training evaluation plans that include the evaluation purpose, relevant questions, and methods of data collection can help improve training programs. Data from formative evaluations, such as pilot or usability testing, can improve or enhance current practices as they are developing. Training effectiveness can be determined by measuring changes in personnel performance and knowledge.

Personnel should be encouraged to provide feedback during training and if possible, after training is completed. All data and feedback received should be analyzed periodically and used for ongoing continual improvement to the training program.

### E2.2. Competence Assessment

Evaluations that directly relate to learning objectives help reinforce training. To ensure quality of repository activities, training programs should include methods to assess the performance of trained personnel, where possible. These methods may include knowledge tests (written or oral), observational evaluations, or practice exercises. Additionally, proficiency testing can help determine that personnel know the proper manner by which to respond to alarms etc.

Feedback should be provided both during and after the assessment exercise to support learning. Any evidence of completion, such as a certificate, digital record (*e.g.*, online score), or competency assessment records, should be documented in the training file (see *E2.4. Frequency of Training*) and aligned to the competence matrix where used (*E2.1.1. Assessment of Training Needs*).

#### E2.2.1. Training Follow-up Support

Continued learning activities and supporting resources can be provided to help maintain retention of knowledge and process skills. A repository should consider developing resources, such as seminars or quizzes, that can be distributed among larger groups to more efficiently provide post-training reinforcement. If training is done across multiple repository sites, the training follow-up support should meet the needs of each location (language requirements, technological limitations).



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## E2.3. Training Program Personnel

### E2.3.1.Trainers

Trainers can be a member of the repository personnel or a repository-approved external training provider deemed competent to conduct the required training. Trainers should be experienced in the regular performance of the procedures and be skilled in explaining all elements of the task. Trainers should be approved by the Training Coordinator (see *E2.3.2. Training Coordinator*). Trainers may require retraining when changes to the content have been approved. 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 may provide the training. Different approaches can be used to enable training. In-person instruction, if interactive, can be beneficial for skill-based training, whereas the use of web-based technologies such as online courses or video conferencing offer flexibility and remote accessibility. Combinations of these methods can also be used, *e.g.*, use of a webinar to communicate new or revised policies and on-the-job or instructional training for updated procedures. Previously recorded training materials may enable personnel to complete training at their own pace when time can be scheduled based on daily activities.

During the training period, the trainer demonstrates, explains, and reviews the practices and 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 or other competent individual (may be a supervisor or a peer) 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. For example, the trainee first observes the trainer performing the procedure, then both trainer and trainee do it together, and finally the procedure is conducted by the trainee under the trainer's observation. This can be repeated several times as needed until the trainer considers the trainee approved to carry out the procedure by itself without supervision.

***BEST PRACTICE:*** Trainers should consider the most appropriate approach for both the students and the material being taught. After the training has been completed, the trainer or a designated competent colleague should be available to answer questions when the task is being performed by the trainee for the first few times.

### E2.3.2. Training Coordinator

The Director should ensure personnel are appropriately trained and that standard operating procedure (SOP) changes are communicated appropriately. The Director may delegate this task to a Training Coordinator or equivalent position. The Training Coordinator should have full access to the last version in force of the list of SOPs for the repository 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 (or equivalent) and with other individuals responsible for specific areas of repository procedures (*e.g.*, shipping and handling). The Training Coordinator is responsible for monitoring, training, and maintaining appropriate training documentation of all personnel, and closely coordinates the training and education documentation with personnel who maintain employee records, as needed. The Training Coordinator maintains records of personnel to be trained in each required area, tracks the time of their periodic updates of training, informs the personnel of potential times of training, and ensures the training is completed according to the required timeframe. An online system can be used to facilitate these functions.

## E2.4. Frequency of Training

Training and repeat training should be conducted in accordance with applicable regulations and in accordance with the needs of the particular tasks and positions held by repository personnel. Regulations sometimes require training before the employee begins working and yearly thereafter (*e.g.*, biohazard and chemical hazard training). Training for repository tasks should be implemented before personnel undertake the tasks. Repeat training should be performed according to a defined schedule described by SOPs. Supplemental training (*e.g.*, 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 improve performance (see *Section D3.8.2. 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.

### E2.5. Training Documentation and Records

Once the training is complete, a written record of the completed training should be made that includes the signatures of both the trainee and the trainer. Electronic signatures can be used for documentation of any electronic training that is received.

A training file should be maintained for repository personnel and should include at least the following:

- Position description including a job title; responsibilities; and the educational, skills, and work experience required.
- Curriculum Vitae or resume.
- Example of the employee's signature and initials.
- Copies of any certificates documenting specialized training, *e.g.*, shipping, safety, and applicable regulations.
- Professional education and diplomas/certificates for specialized positions (*e.g.*, medical director) or those related to operating and providing maintenance for specific machinery and equipment (*e.g.*, pathologist, cryo-engineer, cryo-technician, data administrator) should be assessed.
- Documentation pertaining to personnel review of SOPs pertinent to the position.
- Proof of participation with repository orientation program.
- Documentation of training in alarm response and resolution.
- Documentation pertaining to competency assessment, *e.g.*, checklist or video evidence of task performance.
- Documentation of analytical results to demonstrate continued proficiency in specified technical tasks, *e.g.*, results of reproducibility and/or quality control results.

The training file should be kept in the repository with appropriate protections for confidentiality, privacy, and security (see *Section I2.3. Data Security and Privacy*) and be available for quality assurance review and/or audits (see *Section D3.7. Auditing for Performance Review*). The training file should be archived in accordance with established procedures when personnel leave the organization. If personnel move from the repository to another department within the organization, the training files should be transferred to the new department. For more information on management of records, see *Section D3.2. Documentation Management and Control*.

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# SECTION F: HEALTH AND SAFETY

## F1. GENERAL INTRODUCTION TO HEALTH AND SAFETY

Issues related to safe operation of a repository are complex and depend on the repository's particular activities. Requirements governing Health and Safety (H&S) may be covered by national/federal, regional, or local regulations. Repositories should ensure they have reviewed and comply with applicable regulations regarding health and safety (see *Section C1.2. Legal Implications*).

Each repository should determine which areas of safety are applicable and develop an appropriate H&S plan[1-4] (see *Section A4.4. Operations Plans*). Health and safety plans are used to prevent or to minimize harm to employees, visitors, and the environment. Such plans should address:

- Management commitment to H&S.
- H&S rules and procedures.
- H&S training (see *Section E. Training and Competency*).
- Tracking of H&S performance and improvement within the repository (*e.g.*, documentation of records and use of H&S Key Performance Indicators).

In order to develop an effective plan, the likelihood and source of potential injuries for each person should be identified. These depend upon the procedures and activities undertaken as well as locations in which personnel are likely to spend time[3,4]. Each employee and their 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[1-4]. Identifying risks related to the safe operations should be carried out as an element of an overarching risk management plan (see *Section B. Risk, Emergency, and Disaster Management*). See the World Health Organization (WHO) Laboratory biosafety manual, fourth edition, for guidance on (biosafety) risk assessment as well as risk assessment templates[5].

***BEST PRACTICE:*** Repositories should perform health and safety risk identification, assessment, and mitigation appropriate to repository activities, applying required health and safety measures and regulations.

## F2. SAFETY INFRASTRUCTURE

The Director or other individual with overall responsibility for the organization (see *Section A4.2.1. Repository Oversight*) generally has a legal responsibility for the safe operation of all components of the organization including a repository; however, the day-to-day responsibility for H&S is frequently designated to another individual and/or, for example, to a H&S Committee. While this individual or committee may be primarily responsible, a responsibility for safety also lies with each employee.

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

The H&S Officer establishes a H&S training program in conjunction with the Training Coordinator (see *Section E2.3.2. Training Coordinator*) and monitors and maintains compliance with the program, evaluates incidents and injuries, and recommends changes to the H&S Committee, as needed. H&S training appropriate to roles, together with that mandated by law, should be enabled for all personnel as further outlined in *Section E. Training and Competency* (also see *Section A4.2. Repository Personnel*). It may be necessary to consider health and safety training needs for personnel who utilize offices or other facilities in the vicinity of the repository and are potentially exposed to but unaware of repository hazards. Such personnel may or may not have a formal association with the repository. The H&S Officer works closely with area supervisors to ensure adherence to all safety regulations[2-4].

In the case of repositories with (very) few personnel and limited supervisory capacity, one person may perform more than one role in managing or supervising H&S. Personnel in the host organization or members of the repository's management committee can, where deemed appropriate, fill these roles.

## F3. PERSONAL PROTECTIVE EQUIPMENT

The use of Personal Protective Equipment (PPE) is a risk reduction strategy primarily aimed at protecting personnel and includes wearable equipment and/or clothing and footwear[6]. All personnel, including visitors, should wear appropriate clothing (*i.e.*, lab coats, long trousers/pants, and covered shoes). 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 should be laundered regularly or disposed of depending upon the type and extent of exposure.

Eyes and other mucous membranes, including ears, should be protected from exposure to biohazards and hazards such as chemicals, ultraviolet light, and loud equipment such as compressors and sonicators (see *Section H6. Walk-In Environmental Storage Systems*). Depending on the likelihood of exposure, this protection may be accomplished via goggles, safety glasses, ear defenders, 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 should be individually fitted.

Specialized PPE may be required for particular hazards. For information pertaining to use of cryogens, see *F4.7. Liquid Nitrogen Safety*.

Appropriate safety equipment for specific tasks should be available and used by all personnel as designated in the relevant standard operating procedures (SOPs) (see *Section D3.3.1. Potential Components of an SOP* and *F4. Safety Topics*). Caution should be exerted to ensure that multiple layering of PPE that impacts dexterity does not place personnel at a greater risk of exposure to hazards. PPE and other safety equipment should be placed in an easily accessible and visible location. PPE should be correctly fitted, inspected periodically, and replaced when deemed necessary. Personnel should be trained in the use of PPE relevant to their roles and activities (for further information on training, see *Section E. Training and Competency*) and its use by personnel should be monitored.

***BEST PRACTICE:*** Personnel should use personal protective clothing/equipment, as appropriate, when working within a repository.

## F4. HEALTH AND SAFETY TOPICS

### F4.1. Biorisk Management

Biorisk assessment is an approach that considers the severity and likelihood of a particular adverse

impact resulting from a specific biological hazard. It forms part of the risk management process (see *Section B. Risk, Emergency, and Disaster Management*). Important considerations that form part of the Biorisk assessment include:

- Biosafety level, to assist in evaluation of potential severity of harm.
- Biosecurity that defines controls that reduce the risk related to the loss or misappropriation of biological material.
- Biological containment as a control measure to minimize harm resulting from exposure to biological material.

Definitions of these and other biorisk terms and management processes can be found in ISO35001:2019 Biorisk management for laboratories and other related organizations – Requirements[7].

#### F4.1.1. Biosafety

All specimens, whether fixed, paraffin-embedded, fresh frozen, or freeze-dried, should be considered as potential biohazards. As processing increases (*e.g.*, fresh to frozen to fixed to paraffin-embedded), the relative risk from various infectious agents is usually reduced[3,4]. However, certain agents such as prions (*e.g.*, the causative agent for Creutzfeldt-Jakob [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.*, as if infected with agents that may be pathogenic to humans.

Pathogens can persist in liquid nitrogen (LN2) supplies. LN2 can therefore be a source of transmission of disease and contamination of specimens, and should be treated as a biohazard[8]. For safe handling of specimen containers retrieved from LN2 liquid phase storage, triple washing in certified sterile ultraviolet-treated LN2[9] may prove an effective decontamination solution[10].



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Repositories should develop a Pathogen Exposure Control Plan or similar to eliminate, minimize, or otherwise control occupational exposure to pathogenic organisms. Applicable regulations covering occupational exposure to bloodborne pathogens should be determined and be accounted for within the plan. The plan should include:

- Personnel exposure risk assessment.
- Methods to control exposure, *e.g.*, universal precautions, personal protective equipment, engineering controls.
- Appropriate vaccinations.
- Remedial action for post-exposure evaluation and follow-up.
- Communication of hazards.
- Accurate recordkeeping, *e.g.*, geographical source location (*i.e.*, country, region, city, specific organization), chain of custody, handling personnel.

Repositories collecting and receiving environmental specimens should provide training to minimize exposure to toxic substances. Personnel should receive training in line with the highest biosafety level of the repository so that they can recognize hazards that accompany exposure to harmful compounds and diseases and manage the risk[11], *e.g.*, through use of infection control, disinfection, decontamination and sterilization (see *Section G9. Pest and Contamination Control*).

Disinfectants should be chosen according to their efficacy spectrum and any applicable biocide regulations. The repository should be aware of any limits on use (*e.g.*, corrosiveness, toxicity, and prohibitive costs) and the possibility of resistance development. Repositories should validate biocides and disinfectants used, particularly for cleanrooms. Validation should take into account both the range of microorganisms likely to be found within the repository environment or associated with the specimens procured by the repository as well as the potential for development of resistance. Further information on disinfectants may be obtained from the Centers for Disease Control and Prevention[12]. Air quality of areas considered at risk should be measured and validated periodically with a particle counter (calibrated, multi-channel) to help identify air-propagated contamination sources.

Personnel should consult relevant biosafety manuals (produced by their organization as well as by national, regional, or international external parties with a safety remit[5]) on the properties of pathogens and recommendations for work involving these agents.

### F4.1.2. Biosecurity

In addition to measures to manage risk of accidental exposure, repositories should instigate appropriate biosecurity measures to prevent loss, theft, or (intentional) misuse. These can include restricted access, biocontainment of infectious agents and toxins (*e.g.*, biological safety cabinet, anti-aerosol centrifuges, positive pressure displacement, use of high-efficiency particulate absorbing [HEPA] filters), determination of end-user qualification and use of permit requests (dual use and phytopathogens), and internal or external inspections. A biosecurity policy or plan should be in place to manage any unexpected and/or unidentified material received by a repository and should address appropriate biocontainment including quarantine and/or disposal routes and escalation procedures. Personnel should be trained and deemed competent in all biorisk policies and procedures.

***BEST PRACTICE:*** Personnel at risk of exposure to vaccine-preventable infectious diseases should undertake appropriate immunizations.

### F4.1.3. Biocontainment

A biocontainment or biological hygiene plan should include the following:

- Prevention, containment, and clean-up biological spills.
- Disposal of biological waste in line with regulatory requirements, including specimens and biologically contaminated materials resulting from clean-ups and from decontamination activities.
- Decontamination of storage areas, instruments, and equipment.
- Approaches to ventilation failure, evacuation, relevant medical care, and reporting of biological exposure incidents.
- A description of locations where eating, drinking, storing food and beverages, smoking, gum chewing, and application of cosmetics are prohibited, including areas where specimens are handled and/or stored.
- The use of disposable PPE.
- The use of appropriate biocontainment solutions[13], *e.g.*, a biological safety cabinet with HEPA filters to reduce the risk of exposure to potentially infectious disease.
- Measures to minimize the generation of and exposure to aerosols.

## F4.2. Chemical Safety

Many countries have regulations that govern activities relating to chemical safety that may affect repositories. These laws may mandate that an organization develop a written chemical hygiene plan or to undertake risk assessment relevant to the ordering, storage, use, and disposal of substances deemed hazardous to health. The WHO Human Health Risk Assessment Toolkit: Chemical Hazards can assist with this[14]. The toolkit helps to identify, acquire, and apply the relevant information to help an individual assess chemical hazards, exposures, and related health risks for their activities at local and/or national levels. A repository chemical safety approach 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. A Material Safety Data Sheet (MSDS or SDS) for each chemical should be available for easy access and reference. SDS are available from manufacturers and are generally provided either in hard copy when the chemical is delivered or as a URL for downloading.

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:*** Replace chemicals that are hazardous to personnel or the environment with alternatives when possible.

### F4.2.1. Chemical Safety Approach

A chemical safety approach should include the following[2-4]:

- Approaches to prevent, contain, and clean up chemical spills, including 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 and storage of all chemicals, including those 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.

### F4.2.2. Compressed Gasses

Compressed gasses including argon, carbon dioxide ($CO_2$), $LN_2$, among others can present a risk of asphyxiation by displacing oxygen (see *F4.9. Oxygen Monitoring*). While eye protection might not be required for working with compressed gasses, it is recommended. Employees should wear oxygen monitors while handling compressed gas cylinders or working with compressed gasses. 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. The Compressed Gas Association provides a number of publications and posters related to health and safety associated with compressed gasses[15,16].

***BEST PRACTICE:*** Appropriate protective equipment should be utilized when working with compressed gasses.

***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 gasses should be stored and transported in well-ventilated areas, with detectors and alarms fitted.



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### F4.3. 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 only be performed by competent, qualified electricians ensuring that personnel in the affected work areas are protected during the removal of fuses and while working near a water source. There should 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. Where equipment operates at a nonstandard voltage (*e.g.*, it may have been purchased from another country), corrective measures such as correct wiring connections should be determined and put in place to ensure a supply of the correct voltage.

Persistent incorrect voltage conditions can result in overheating of the wiring or components and possible failure or fire. Where necessary, in order to ensure a safe, continuous, stable voltage supply, a repository should consider solutions such as uninterruptible power supplies (UPS), surge protectors, or voltage regulators. Routine checks of facility voltages and/or noting of prolonged use of such solutions will alert electrical personnel 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.

### F4.4. 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, fire drills should be conducted and fire suppression equipment and safety showers/eyewash 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 should be prioritized during purchase. Smoking, if permitted, 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 is governed by national/federal, regional, and local requirements. For additional information see *Section G8. Fire Prevention*.

***BEST PRACTICE:*** Fire safety should be an important component of an organization's health and safety plan.

### F4.5. 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 (*e.g.*, during collection of specimens; see *Section J4. Collection Considerations*). 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.

Repetitive-motion and back ailments resulting from incorrect lifting and other movements are also among the causes of physical injuries. Repository personnel may be required to stand on stepstools and lift heavy racks vertically out of the freezer in order to access specimens. The potential from harm can be reduced by conducting ergonomic assessments of each person's specific work environment (including shared workstations) to identify potential risks and make appropriate adjustments, *e.g.*, improved positioning of objects and provision of the necessary tools. Strategies such as installation and use of assistive technologies to aid with cumbersome or repetitive activities, *e.g.*, removal of the racks from the freezers during an emergency, can be considered to help to avoid injuries. Correct application of ergonomics in the work environment helps ensure that 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 (see *Section H4. Automated Storage Systems*). Ergonomics should be considered when developing a repository or organizational H&S 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 H&S plan 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). 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 health and safety plan.

#### F4.5.1. Lone Working

A lone working policy should be in place for personnel working alone or out of normal working hours. This should limit access to hazardous areas in the repository during off-peak hours (see *Section G7. Security and Access*) and ensure that nobody is alone in such areas for more than a few minutes without their welfare being assured. The repository should provide suitable PPE including wearable automatic warning devices (*e.g.*, low oxygen detection, panic, tilt, or no movement alarms). These devices should be linked to security systems for alerting responders and security personnel during out-of-hours working and call-outs, and when working in low-footfall or hazardous environments (see *F3. Personal Protective Equipment*).

***BEST PRACTICE:*** Lone worker alarms should be used in addition to personal $O_2$ monitors when accessing $LN_2$ storage areas unaccompanied.

#### F4.5.2. Safety in Walk-in Units

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 a personnel monitoring system be used 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, many organizations make use of a buddy system. Wearable devices such as those commonly used by firefighters and other emergency personnel and/or motion detectors permanently installed in the system should be used to detect motion of personnel working in the system (see *F4.5.1. Lone Working*). 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. If dry ice is used, there should be adequate ventilation to ensure that sufficient air or oxygen levels exist (see *F4.8. Dry Ice and Carbon Dioxide Safety*). 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 (see *F4.9. Oxygen Monitoring*). Similarly, it is not appropriate to use scientific cold rooms to store hazardous or flammable material or food for consumption.

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. For further information on walk-in units, see *Section H6. Walk-In Environmental Storage Systems*.

***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 sign (see *F4.10. Safety Signage*) should be posted at the entrance of walk-in cold storage areas advising that the area may be slippery.

### F4.6. 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 personnel 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.



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## F4.7. Liquid Nitrogen Safety

Additional safety precautions are needed when using $LN_2$. Displacement of oxygen, extremely cold temperatures, and the rapid rate of expansion when exposed to ambient conditions pose increased risks to personnel. PPE including alarm-alert devices designed to mitigate this risk should be worn at all times when handling cryogens (see *F3. Personal Protective Equipment*) and personnel should be trained and deemed competent in its use as per their training records. Relevant procedures should describe the potential health hazards and required safety precautions, and should include training using related SDS.

Methods of seeing into the $LN_2$ storage facility are helpful for external visual inspection of $LN_2$ storage units, as well as determining personnel status or wellbeing. Viewing windows, curved mirrors and cameras, when properly positioned, can assist in determining if anyone has collapsed in the facility and is on the floor (due to low oxygen or other issues). Additionally, internal doors and walls may have transparent glass areas to enable visual inspection.

***BEST PRACTICE:*** Those working with or around liquid nitrogen and other cryogens should use appropriate protective equipment.

The risks associated with liquid nitrogen are threefold: cold burns, asphyxia, and explosion. These are addressed below.

### F4.7.1 Cold Burns

The extremely low temperatures generated by liquid nitrogen can cause cold burns to the skin both from the liquid itself and from materials that have been immersed in the liquid or vapor phase of liquid nitrogen immediately before handling. The following PPE is recommended:

- Eye protection every time $LN_2$ is handled. A full-face shield to protect the eyes and face from splashes when working with large volumes of $LN_2$ (*i.e.*, when pouring or filling). At other times, unvented safety goggles to be used.
- Cryogenic gloves for handling anything that is or has been in recent contact with $LN_2$. Cryogenic gloves are designed to be used in the vapor phase of $LN_2$ only and should not be immersed in liquid nitrogen under any circumstances. They should be loose-fitting so they can be removed quickly if soaked with liquid nitrogen. Disposable gloves can be worn underneath shared cryogenic gloves for added hygiene.
- A long-sleeved, buttoned lab coat when working with $LN_2$ to protect the body.
- Non-absorbent cryogenic aprons when handling large volumes of liquid nitrogen. These may also be used where splashing is likely to occur.
- Shoes which cover the entire foot and be sturdy and non-absorbent.

Avoid clothing with open pockets and turn-ups/cuffs where liquid may collect. Open-toed shoes or sandals should also be avoided.

### F4.7.2. Asphyxiation

Nitrogen is odorless, colorless, and tasteless. As $LN_2$ evaporates, the rapid rate of expansion reduces the oxygen concentration in the air and even a 2.5% depression of $O_2$ levels creates a potential for asphyxiation. This risk should not be undermined, particularly for confined spaces. The following PPE is recommended:

- Both fixed and mobile/personal monitors may be appropriate depending on the size of the facility and volume of exposure.

Even when fixed oxygen monitoring units are installed, the use of personal oxygen monitors (see *F4.9. Oxygen Monitoring*) is recommended when:

- Accessing large liquid nitrogen freezers.
- Manually filling liquid nitrogen Dewars or small liquid nitrogen freezers.
- Working for long periods in the vicinity of $LN_2$.

This precaution is advised due to the potential for the creation of localized, low-oxygen environments during these operations.

### F4.7.3. Explosion

Liquid nitrogen expands rapidly when exposed to ambient temperatures. This expansion, if contained, can cause a rapid build-up of pressure causing glass, thin metal, and plastic specimen containers to shatter. Certain containers, like cryogenic straws, bags, and some vials, are hermetically sealed and pose less risk for storage of specimens in the liquid phase of nitrogen. A risk for $LN_2$ ingress into any container should be considered. The following is recommended:

- Face and eye protection are recommended when handling vials removed from a $LN_2$ freezer even where specimens have been stored in the vapor phase.

- Cryogenic gloves should be worn to protect hands when handling specimens stored at cryogenic temperatures.
- Specimen container caps can either be loosened (or uncapped when intended for disposal) or containers can be moved from the liquid phase to the vapor phase in preparation for extraction from the storage unit. This avoids pressure buildup within the container and potential explosions.

***BEST PRACTICE:*** Personnel working in areas where $LN_2$ is being used (including non-repository personnel) should be made aware of potential hazards and trained in appropriate documented health and safety policies and procedures.

***BEST PRACTICE:*** Appropriate safety PPE, including personal oxygen monitors, should be used when dealing with liquid nitrogen and other cryogens.

***BEST PRACTICE:*** $O_2$ monitoring should be installed in any areas of the facility where $LN_2$ is utilized.

***BEST PRACTICE:*** Only specimen containers designed for $LN_2$ use (see *Section J3.3. Specimen Containers*) should be used for storage in $LN_2$ given that many commercially available specimen containers are penetrable by liquid nitrogen and can create an explosion hazard.

***BEST PRACTICE:*** Unauthorized access to $LN_2$ specimen storage areas should be prevented through use of controlled access.

## F4.8. Dry Ice and Carbon Dioxide Safety

Those working with dry ice (solid $CO_2$) should use appropriate protective wear approved for low temperatures to avoid skin damage. The use of solid $CO_2$ should be prohibited in enclosed or non-ventilated areas (see *Section F4.5.2. Safety in Walk-in Units*). Dry ice sublimates into large quantities of carbon dioxide ($CO_2$) gas.

$CO_2$ 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. Personnel should wear personal oxygen monitors (see *F4.9. Oxygen Monitoring*) while handling $CO_2$ cylinders or working with $CO_2$ gas, or for extended use in close proximity to dry ice. 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.

Further information on dry ice use in shipping is provided in *Section L2.2.1 Shipping Temperature*.

## F4.9. Oxygen Monitoring

Adequate ventilation and monitoring are both critical controls in repositories where liquid nitrogen and/or dry ice are used. Because gaseous nitrogen and carbon dioxide both displace oxygen, care should be taken when using $LN_2$, $LN_2$ storage units and/or dry ice. The risk is inversely correlated with the size of the area. The normal level of oxygen in ambient air is ~21%. When oxygen levels drop (*e.g.*, due to tripping of pressure relief valves, nitrogen gas plumes when filling Dewars), they may fall below the threshold necessary to sustain life[17]. Oxygen levels of less than or equal to 19.5% and/or dizziness should prompt evacuation. Oxygen monitoring should be in place installed by a professional company in any areas of the facility where oxygen-depleting substances are used (see *Section G3.2. Air Flow, Circulation, and Humidity*). Both fixed and mobile/personal $CO_2$/$O_2$ monitors may be appropriate depending on the activities conducted and the size of the facility.

Signage accompanying all oxygen monitors should clearly explain what the alert is for and the potential risks (see *F4.10. Safety Signage*). Personnel should be trained and deemed competent (see *Section E. Training and Competency*) to follow established protocols for alarm alert settings, evacuation, and safe return to the facilities after evacuation. In the event of an $O_2$ depletion, the alarm should sound, and the facility should be evacuated immediately. The area should not be entered for any reason (*e.g.*, investigate the cause of the alarm) until normal $O_2$ levels are restored. Only emergency services personnel wearing appropriate breathing apparatus should be permitted access to remove any casualties. Failure to observe such precautions can lead to (further) casualties.

All $O_2$ or $CO_2$ monitoring devices whether fixed or mobile degrade over time, leading to inaccurate readings. Sensors should be inspected and tested regularly and replaced under a program of planned preventative maintenance according to the manufacturer's guidelines (see *Section H12.1. Equipment Preventative Maintenance and Repair*).

***BEST PRACTICE:*** Personnel should carry personal oxygen monitors when working in areas where liquid nitrogen, $CO_2$, or other potentially $O_2$-depleting gasses are used.



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### F4.10. Safety Signage

A safety sign provides information about safety or health and can be a signboard (provides information or instruction using a combination of shape, color, and symbols but excludes information in writing), printed label, color, acoustic signal, verbal communication, or hand signal. The symbols or pictograms on a signboard are intended to be understood, independent of the language ability of the viewer. Supplementary text can be provided separate to the signboard (which should not be altered) and in the vicinity of the signboard. The meaning and requirements of any signs used should be provided during training (see *Section E. Training and Competency*).

***BEST PRACTICE:*** Safety signs (relevant to the hazard or danger) should be used throughout the facility whenever a hazard or danger cannot be avoided adequately or reduced in another way. Signs should be posted indicating the use of proper protective equipment and the need to follow established safety procedures.

### F4.11. Environmental Safety and Sustainability

Along with local chemical and related biosafety regulations and considerations on the environment, repositories should plan and operate with awareness of environmental sustainability and impact (see *Section C1.5. Environmental Impact and Biobanking*). In some cases, organizational or local policy or regulation require environmental impact evaluation. Increasingly, equipment (*e.g.*, cold-storage units) that offer improved energy efficiency are available and may additionally offer a long-term cost saving opportunity (see *H1. General Introduction to Storage and Processing Equipment*). Where repository personnel conduct field work (*e.g.*, collection or survey within natural habitats), environmental impact should form an important part of operational and experimental design. Consultation with local environmental protection laws, permits, and/or indigenous groups may be necessary or required.

***BEST PRACTICE:*** Repositories should implement favorable environmental sustainability operations where possible to reduce potential adverse impacts on the environment.

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# SECTION G: FACILITIES

## G1. GENERAL INTRODUCTION TO FACILITIES

When planning a facility many factors need to be considered to ensure that specimens and accompanying data are stored appropriately. The facility should provide a safe and effective working environment (see *Section F. Health and Safety*) and meet the needs of the repository[1]. To inform the needs for planning the design of a repository, it is necessary to first determine its purpose and objectives (see *Section A. General Introduction to Repositories*). Among the factors that influence repository design are:

- The types of specimens and data to be stored.
- The associated biorisk (see *Section F4.1. Biorisk Management*).
- The proposed or mandated retention period (see *Section A1.1. Types of Repositories*).
- The projected growth in specimen numbers.
- Specimen and data fitness for purpose (see *Section D1. General Introduction to Quality Management*).

These impact facility space requirements, not only for the safe movement of personnel and equipment, but also for specimen storage.

Where liquid nitrogen storage is required, consideration should be given to the associated infrastructure (bulk liquid nitrogen tank, vacuum-insulated pipework, air handling systems, etc.) required to support this type of storage with its resulting space and cost implications (see *G11. Cryostorage*).

The repository should consider the anticipated levels of movement of specimens and data (see *Section I. Information Management*) to and from the storage facility when planning storage capacity. Where possible, specimens should be stored in dedicated, secure storage units to avoid potential cross-contamination or compromised storage conditions (*e.g.*, accidental thawing). The size and number of storage units should be matched to the prospective size of the repository collections and the type of specimens to be stored. The repository should account for future expansion of the collection, where practicable. Off-site storage may be considered where storage capacity is limited by external factors or is desired. This can be facilitated through agreements with other similar repositories or with a commercial third party (see *Section A4.3. Contracting Services and Consultants*). In either case, the facilities offered should be reviewed for compliance with requirements for safe and effective specimen and data storage (see *Section D3.4.3. External Quality Assurance*).

Off-site storage or physical separation of specimens should also be considered as part of disaster recovery plans (see *Section B2. Business Continuity Management*). This should also include other backup systems that are critical for maintaining specimen integrity and quality. Backup systems to consider should include, but are not limited to:

- Water.
- Power, *e.g.*, generators, uninterrupted power supplies to commence an alternate power supply (see *G6. Power*).
- Fuel for backup generators (see *G6. Power*).
- Heating, ventilation, and air conditioning (HVAC) of the ambient environment and any data center components.
- Communication systems (including building support and equipment monitoring systems).
- Liquid nitrogen ($LN_2$) supply (see *G11. Cryostorage*).

When designing complex systems, especially those related to HVAC (*e.g.*, cleanrooms and containment suites) and $LN_2$ (*i.e.*, delivery and storage facilities), specialist external design and construction consultants should be approached for advice (see *Section A4.3. Contracting Services and Consultants*).

Facility location is of particular importance, both with respect to the potential for the environment to impact the facility (*e.g.*, vicinity to waterways, climatic impacts) and vice versa. For example, basements and other low-lying locations may be at a greater risk of flooding during unexpected events[2]. An environmental impact assessment should be conducted as part of the design process to determine the impact of the facility on the surrounding environment during routine operations. Special attention should be focused on the placement of supply tanks (*e.g.*, $LN_2$, generator fuel) that may be located external to the facility, as well as ventilation systems.

It is recognized that it is not always possible to design facilities from the ground up. Some repositories use or repurpose existing buildings and/or share facilities with other groups or organizations. Where a central facility has multiple users from different groups, it may be challenging to implement best practices. Where possible, a review of proposed shared facilities should be undertaken considering features that would be incorporated for a new build to ensure that specimens and associated data are not compromised by other users/procedures of the shared facility. Risk identification and assessment should be conducted and


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documented (see *Section B1. Risk Management*), and processes to mitigate identified risks (*e.g.*, emergency handling, cross contamination) should be put in place. A disaster recovery plan should be established for the repository (see *Section B2.2. Business Continuity Plan*).

The review should be used to collaboratively identify areas where improvements can be made to ensure a safe and effective processing and storage environment for all repository specimens (see *Section D3.4. Quality Assurance Approaches*). It should be inclusive of policies, protocols, and safety measures and should be conducted in such a way that all groups within a shared facility contribute to the review and agree on the outcomes. In these and other circumstances, a repository may need to accommodate additional heightened control measures and associated protocols (*e.g.*, engineering controls) to facilitate safe operation (see *Section F. Health and Safety*), especially where $LN_2$ is used for cryogenic storage.

***BEST PRACTICE:*** Repositories should ensure appropriate infrastructure and resources (including facilities, equipment, and personnel) are available to support the services offered.

***BEST PRACTICE:*** Where a facility is not purpose built, but is shared or inherited, a review of the facility should be undertaken to identify aspects or areas that may need improvement to ensure safe practice and integrity of specimens and associated data.

***BEST PRACTICE:*** Facility planning for a repository or a relocation (see *G10. Relocation of a Repository*) should consider the environmental conditions experienced by the region where the facility is to be located, the local supporting infrastructure and supply chains available for needed resources (*e.g.*, power, liquid nitrogen).

## G2. SPACE

Adequate space should be allotted with sufficient clearance per manufacturer recommendations for safe operation, routine verifications, maintenance, and cleaning of all equipment. This includes equipment for reception, processing, storage (as well as backup storage; see *Section H9. Backup Storage Capacity*) and distribution or shipping as well as auxiliary equipment such as air conditioners, monitoring, and safety equipment. Spatial needs include the placement area, height clearance of the equipment, and general clearance for specimen handling, including the addition and removal of any inventory racks in storage units. Consideration should be given to the width and height of all doorways, hallways, elevators, and any pass-through between the loading dock and storage location or laboratories. The physical layout of larger storage units should be arranged to facilitate unit removal without recourse to movement of other such units in the vicinity. There should be sufficient space outside the repository (*e.g.*, for access, road structure, loading dock, or adequate parking) for receiving and sending of shipments and for deliveries, *e.g.*, of $LN_2$ that might require outsized or specialized vehicles.

Sufficient space to accommodate separate storage units to enable the division of multiple aliquots of critical specimens for safekeeping should be considered. This may include a decision to accommodate specimens across different physical locations to subvert catastrophic loss in the event of a destructive disaster. A risk assessment (see *Section B1. Risk Management*) can help to evaluate the need for this approach.

Facility and space management can benefit from a comprehensive list of utilities and a graphic showing where each can be accessed along with any spatial requirements pertaining to equipment housed.

## G3. VENTILATION, TEMPERATURE, AND HUMIDITY

### G3.1. Facility Temperature

In most repositories, it is recommended to maintain temperature within defined limits. Sufficient heating capacity should be provided to prevent the freezing of water in drain lines. Likewise, air should be sufficiently cool or actively cooled (using air conditioning or alternative less-energy-demanding systems). This can assist with ergonomics (*e.g.*, personnel comfort when using personal protective equipment [PPE]) and prevention of contamination or excessive load on equipment such as compressor systems. Control of air flow and humidity is additionally important (see *G3.2. Air Flow, Circulation, and Humidity*).

***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.

### G3.2. Air Flow, Circulation, and Humidity

Air circulation is a critical component of facilities design of repositories. Sufficient air circulation should be provided to prevent excess moisture and condensation where freezers are located. Excess humidity, if left unchecked, can lead to fungal or mold growth, corrosion on equipment, and ice build-up on pipes and valves (see *Section H7.1. Humidity Monitoring*). This may directly or indirectly affect specimen integrity, damage stored consumables, and cause health problems (see *G9. Pest and Contamination Control*). Sufficient space for air circulation is required where mechanical freezers and refrigerators are located to prevent excess heat accumulation which may negatively affect compressor function (see *Section H3. Mechanical Freezers*).

Air circulation and humidity should be managed to minimize air passing over the opening of a liquid nitrogen storage unit to avoid accelerated nitrogen boil off and reduce the risk of contaminants entering the vessel. Adequate ventilation and monitoring are critical in repositories where liquid nitrogen and dry ice are used to ensure that sufficient oxygen levels are maintained (see *Section F4.9. Oxygen Monitoring*). Specific requirements for regular and emergency ventilation for $LN_2$ storage areas exist in some countries.

When activities generating potentially harmful vapors (*e.g.*, formaldehyde) are undertaken, the ventilation system should be sufficient to control exposure and undergo frequent checks for damage, in addition to routine testing and examination, to ensure effective operation. Where fumigation is planned, the high levels of toxic fumigant will require more rigorous risk assessment and applicable regulations and local rules and procedures for ventilation should be adhered to. Where a facility is being fumigated appropriate seals should be in place to prevent leakage into other areas and at its termination, air ventilation should be adequate to make the storage environment safe for personnel to enter. A dedicated exhaust system interlinked to oxygen monitoring sensors (see *Section F4.9. Oxygen Monitoring*) should be in place where oxygen levels might drop or harmful gasses might accumulate. Low-oxygen alarms should be interlocked to the door to prevent access by unauthorized personnel where warranted to mitigate the risk to personnel (see *Section F1. General Introduction to Health and Safety*). These systems should be installed by a professional company (*e.g.*, a bulk gas supply company).

Consult the manufacturer for recommendations to determine the number of sensors needed. Factors include room size, placement in the room, and height of wall mounting. Adjustments may be necessary to compensate for high altitudes, *e.g.*, automatic pressure correction by means of an integrated barometric pressure sensor or adjusting the oxygen level using a lookup table or a separate pressure sensor. Acoustic and visible alarms should be installed inside and outside the room and dedicated exhaust ventilation should be used in coordination with the sensors.

***BEST PRACTICE:*** When potential for low oxygen exists, appropriate monitoring devices (*e.g.*, oxygen and/or carbon dioxide monitors) with auditory and visual alarms should be combined with a dedicated exhaust system. The system should provide a sufficient flow of air to replace the air volume of a room according to the local regulations. Air should not be recirculated. Air extracted should be ventilated externally, in line with applicable regulations.

***BEST PRACTICE:*** All monitoring systems for measuring oxygen-deficient atmospheres should be installed and evaluated per the manufacturer instructions.

***BEST PRACTICE:*** Duplicate emergency systems (*e.g.*, wall-mounted gas sensor systems linked to a dedicated air exhaust system, automatic emergency fans, automatic door opening, personnel monitoring system) should be used to ensure the highest level of personnel protection.

***BEST PRACTICE:*** Repositories located in areas where humidity is high should have a de-humidification system in place.

## G4. LIGHTING

### G4.1. General Lighting

While the parent organization is often responsible for the lighting infrastructure, the repository should assess that the light available is sufficient to provide a safe working environment (see *Section F. Health and Safety*) and to facilitate correct storage and retrieval of materials, including specimens. The lighting levels required depend on the spatial environment where specimens are stored, the type of activity, the volume and specimen type, and the identification/labeling system used. The repository should consider lighting solutions (*e.g.*, occupancy or motion sensors) in spaces where automatic shutoff could endanger occupant safety or security.

Lighting may be both general and task-focused, depending on the situation. Caution should be exercised to account for any materials or specimens which may be sensitive to light.

***BEST PRACTICE:*** Appropriate lighting should be planned for and used during the storage and handling of materials or specimens, particularly for those deemed to be sensitive to certain lighting conditions.



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***BEST PRACTICE:*** Walk-in freezers and coolers should be equipped with occupancy or motion sensors to enable reactivation of internal lights on automatic or delayed shutoff after door closure.

### G4.2. 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 specimen integrity or the storage conditions (see *Section J3. Specimen Integrity*). For example, the heat from incandescent lighting placed too close to stored specimens may cause thaw, partial thaw, or melt. Light-emitting diodes (LEDs) are more energy efficient, cost effective, and may be useful to direct beams of light for workstations.

***BEST PRACTICE:*** Lighting that does not create a source of heat (*e.g.*, LED lighting) should be used when task lighting is required near work areas used to handle specimens.

### G4.3. Emergency Lighting

In case of power loss, it is critical that emergency lighting is 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.

## G5. FLOORING AND STRUCTURAL SUPPORT

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 and may harbor difficult-to-remove-contamination. Repositories should consider providing anti-fatigue mats in areas where personnel stand for prolonged periods of time.

The combined weight of the storage and other equipment (*e.g.*, freezers, $LN_2$ units, walk-in units) should be taken into account when situating the repository within a building or when designing a new facility. Seismic bracing may be required for $LN_2$ storage units, supply tanks, and/or piping systems as well as pad position and construction for bulk tanks. Local guidelines and regulations for seismic bracing should be followed.

## G6. POWER

Repositories that store specimens in constant temperature environments use equipment that requires a source of constant and stable (*e.g.*, consistent voltage per manufacturers' instructions) electrical power. Even $LN_2$ storage units that do not rely on electrical power for cooling require power for monitoring, alarms, and replenishment of $LN_2$ for auto-fill systems.

### G6.1. Backup Power Supply

A backup power system is strongly recommended in case of interruption to commercial power supply. This system should be sufficient to cover the power consumption of critical equipment (*e.g.*, storage, monitoring, HVAC, and operating or matching backup storage; see *Section H9. Backup Storage Capacity*). This should also include sufficient monitoring and alarm capabilities to last through weekends or any period when the facility is unattended. When using $LN_2$, the backup power or battery backup power source should be capable of providing a complete filling cycle.

***BEST PRACTICE:*** Repositories should confirm that at least all circuits providing power/cooling to critical equipment or the entire facility are on the backup power/cooling system. Where a repository has responsibility for their backup generator, the location should be documented.

#### G6.1.1. Uninterruptible Power Supply

An uninterruptible power supply (UPS) is inserted between the source of power (typically commercial utility power) and the load it protects. When a power failure or abnormality occurs, the UPS will effectively switch from utility power to its own power source or to the backup power source almost instantaneously to provide a continuous supply of electrical power during transition to an alternate power source or orderly shutdown. If used as the source of backup power, the UPS should have sufficient power to complete one fill cycle when using $LN_2$. Power outlets protected by a UPS should be clearly marked and differentiated from non-USP outlets. The limitations of UPSs (*e.g.*, battery life) should be known, and a process in place to ensure that any electrical equipment is safely shut down or otherwise protected before any backup power source is exhausted.

***BEST PRACTICE:*** Computer systems and electronic systems, such as environmental monitoring systems, safety systems (*e.g.*, oxygen sensors, ventilation systems), and controllers for liquid nitrogen freezers, should be protected by a UPS. UPSs used in repositories should be tested annually to ensure backup capabilities.

### G6.2. Generators

The most common type of backup power is a motor generator. Generators provide an alternative source of power when the commercial power supply is interrupted. Generators are typically fueled by diesel, natural gas, or propane. Manual transfer switches, in addition to automatic transfer switches, can be installed for rapid disconnection, so that portable generators can be connected in a matter of minutes. 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.

The generator should be determined based on a risk assessment of the facility, region, and resources (see *Section B1. Risk Management*). Outage scenarios and desired outcomes should be evaluated in advance to ensure the necessary infrastructure is in place. For large repositories, risk assessment informs the decision to have one large generator or multiple smaller ones to support the facility. Based on risk tolerance and financial stewardship, it may be concluded that a backup generator supports only equipment deemed critical. Generators should be located in accordance with manufacturer's requirements and situated a safe distance from doors, windows, vents, and flammable sources.

***BEST PRACTICE:*** A generator should have a fuel supply to run continuously for a minimum of 48 hours and preferably for a minimum of 72 hours, with an ability to refill fuel storage supplies.

***BEST PRACTICE:*** Repositories that utilize generators should have an established fuel management plan for replenishing fuel supplies, including in the event of an emergency. This plan should include lists of suppliers and backup suppliers committed to providing the fuel to the repository as a priority, as needed (see *Section B2.3.3. Procedural and Operational Preparedness*).

#### G6.2.1. Generator Tests

To increase 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. Testing should ensure that any delay between grid power failure and backup systems starting does not adversely impact equipment performance or cause automatic shutdowns.

Load tests should be performed to ensure that the generator functions within specifications under full load. When load testing places sensitive equipment at risk, the generator should be tested less frequently or the sensitive equipment should be isolated before testing. Systems with an automatic transfer switch should also be tested according to manufacturer recommendations. No-load testing should be performed more frequently than load testing. Facilities using bulk diesel storage should perform annual testing and, where necessary, fuel filtering to ensure that excess water or bacterial build-up has not occurred. In cold climates, winterized diesel should be considered.

Testing should be performed by appropriately trained and competent personnel, such as site-wide maintenance personnel (for repositories embedded in larger organizations) or through contracted services (for stand-alone repositories) as part of planned preventative maintenance. In-house testing should only be undertaken by suitably trained and qualified personnel. Testing frequency should follow either the equipment manufacturer's recommendations, that of the parent organization, or applicable regulations or guidance where these exist.

***BEST PRACTICE:*** The back-up power system should be included in a planned preventative maintenance schedule that includes regular testing based on manufacturer or parent organization recommendations.



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***BEST PRACTICE:*** Repositories located in or associated with larger facilities (*e.g.*, hospitals, universities) that automatically initiate backup power upon power interruption should link critical equipment to these emergency systems, where feasible. The operational safety and testing should be performed by professional personnel of the parent organization.

***BEST PRACTICE:*** For large facilities, staging the sequence of mechanical freezer (and other systems) start-up 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 (text, email, phone call, etc.) should be in place to trigger an emergency response.

## G7. SECURITY AND ACCESS

Repositories should be equipped with a system(s) that adequately limits access to personnel 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 biocontainment storage equipment that can be individually secured should be used to store specimens considered valuable, sensitive, or of a biosecurity concern (see *Section F4.1. Biorisk Management*).

### G7.1. Infrastructure for Specimen Integrity Monitoring

Consideration should be given to the use of reliable cellular and/or wireless internet reception in the repository. Storage units, supporting systems (*e.g.*, temperature monitoring systems), and instruments may require cellular or internet connections for alarm notifications. Using wired connections or local repeaters can assist with a reliable network connection in buildings or rooms with insufficient reception and also provides additional personnel safety.

***BEST PRACTICE:*** Repository security systems should be monitored for triggering an appropriate response (see *Section B2.3.1. Organizational Preparation and Action Planning*) to alarms 24 hours per day and seven days per week.

### G7.2. Intrusion Detection Systems

A repository should use basic security systems to ensure protection of the specimens and data stored therein. 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.

### G7.3. Visitor Access Policy

An access policy should be developed for individuals visiting the repository. Where feasible and appropriate, sign-in sheets or logbooks 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 that they have been formally received and their presence *documented*. Visitors should be accompanied by repository personnel at all times during their visit, or in the case of extended professional visits by researchers or others, onboarding and safety training should be provided (see *Section E. Training and Competency*).

***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.

## G8. FIRE PREVENTION

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, extended, or renovated. For information on fire safety, see *Section F4.4. Fire Safety*.

## G8.1. Fire Prevention Plan

Repositories should have a written fire prevention strategy or plan (see *Section A4.4. Operations Plans*) based on a fire risk assessment, including prevention, detection and warning, and emergency routes. The plan should address procedures for:

- Regular maintenance on all equipment used to prevent or control sources of ignition or fires and name or job title of personnel responsible for maintaining the equipment.
- Correct storage of chemicals including solvents (see *Section F4.2. Chemical Safety*).
- A description of any pathogenic and chemical materials held and their storage location should be available for fire service personnel to consult.
- Personnel fire safety training.
- Good housekeeping (*e.g.*, keep work areas clean and uncluttered, returning chemicals to storage as soon as possible, keep general areas free of clutter at all times, particularly corridors and emergency exits).

***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.

## G8.2. 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.

## G8.3. Fire Extinguishing/Suppression Systems

### G8.3.1. 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.

### G8.3.2. 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 personnel 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 released chemical 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 gasses 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.



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## G9. PEST AND CONTAMINATION CONTROL

Insects, mites, rodents, or other small animals may invade the repository space, for example, through drainage systems, windows, etc. If detected, invasion pathway(s) need to be investigated and measures taken to help with problem areas, *e.g.*, seeking advice from a pest control expert. Regular cleaning regimes are recommended, particularly for damp areas and those that collect detritus and dust. The discharge location of dust, vapors, and fumes should be carefully considered to prevent contamination and cross-contamination.

A repository should have a cleaning policy that details and documents those responsible for cleaning, the frequency for cleaning, and specific procedures for cleaning of surfaces and equipment. The cleaning schedule should be based on a risk assessment of contamination. Procedures should be in place for cleaning of restricted access areas and workspaces to be performed by repository personnel. Records of cleaning (*e.g.*, cleaning checklists or cleaning logs specifying location, date, and clean description - routine, deep clean, etc.) should be completed and retained for inspection. Use of antimicrobial cleaning agents may need to be rotated regularly to reduce the chance of resistant strains evolving (see *Section F4.1.1. Biosafety*). Sticky mats can be placed before access doors to reduce the ingress of dust from shoes. Consideration should be given to monitoring for contamination (*e.g.*, mold, mildew, and fungal) in high-humidity areas (*e.g.*, facilities and controlled storage environments; see *G3.2. Air Flow, Circulation, and Humidity*). Maintaining a relative humidity level in the region of 50-55% within the facilities may reduce the potential growth risk for mold, fungi, and mites. Remedial actions should be part of a Pathogen Exposure Control Plan to address any contamination issues that arise (see *Section F4.1.1. Biosafety*). Prior to applying corrective measurements, *e.g.*, fumigation, the potential risk to stored specimens, facilities, and equipment should be evaluated in depth. Whenever possible, and if the specimens are not contaminated or infested, the specimens should be moved to a clean, pest- and contamination-free space prior to fumigation. Fumigation itself should be performed only by professional companies.

***BEST PRACTICE:*** A plan for effective and environmentally sensitive approaches to pest and contamination management should be in place and executed.

## G10. RELOCATION OF A REPOSITORY

There are times that require repositories to relocate to a new site. Such situations may occur for a number of reasons, such as inability to renew a lease, a change in spatial requirements, moving to a new storage platform (*e.g.*, from a manual to automated storage), or in response to an emergency. Relocation may be long term in nature or may be temporary and be additionally followed up by a return to origin or a further new location. Further information covering transfer of specimens and data is provided in *Section K4. Transfer and Disposal*.

### G10.1. Relocation Plan

A plan for relocation should be established and tested to enable successful relocation in the event of an unanticipated emergency (see *Section B2.3. Emergency Preparedness and Response Planning*) as well as a planned event. Since many factors need to be considered, planning should begin as early as practicable to ensure an orderly and effective relocation. A relocation plan should address at least the following aspects:

- Requirements for the new space, documented and complete, addressing anticipated growth for the planned duration of occupation.
- Review of critical processes in the context of the new site to ensure that they can be implemented efficiently. A list of materials to be relocated might necessitate a review of specimens, data elements, storage equipment, and ancillary support systems. A map of the new site indicating the location of all equipment and inventory that will be relocated should be created.
- Resources needed including:
  - Financial costs of relocation (see *Section A3.2.2.4. Relocation or Termination Costs*).
  - Trained and competent personnel for relocating and for handling the collections within the new location (see *Section L2.1. Shipping Regulatory Requirements* and *Section E. Training and Competency*).
  - The packaging for specimen movement, shipping, or specialized transport to conduct a relocation independently or engagement of commercial vendor(s) providing such services (see *Section L. Packaging and Shipping*).
  - Monitoring devices to document specimen integrity throughout relocation (*e.g.*, cold chain). For temperature sensitive collections, and when dry ice containers or liquid nitrogen dry shippers are used, careful planning is

needed to ensure the temperature and integrity of the specimens is maintained during relocation (see *Section L2.2.1. Shipping Temperature*).
  - Storage equipment requirements in excess of what already exists.
- Stakeholders engagement and agreements
  - For relocation of specimens and data inventory to another party's facility/custodianship, a Material Transfer Agreement (MTA) should be executed detailing relocation, rights, and future use of specimens and data including restrictions (see *Section K3. Transfer Agreements*). Where the specimens and data are owned or provided by parties other than the repository, those parties should be notified of the planned relocation (see *Section C. Ethical, Legal, and Social Implications*).
  - Repository personnel should be involved in discussions to ensure that all details are attended to during preparation and execution of the relocation.
  - Responsibilities for each part of a relocation plan should be assigned and agreed upon by each of the various stakeholders involved, including regulations for movement of hazardous and infectious materials.
- Mechanisms for transfer of data associated with the collection, where necessary (see *Section K4.2.2. Data Transfer)*.
- Scheduling of relocation should occur over a period of time for development of effective responses to any challenges that may arise.

Careful planning and organization are recommended to coordinate all parts of the relocation. The plan should ensure that specimen inventory location is known throughout the entire process. The specimen inventory should be verified pre- and post-relocation (see Section J6. Receiving Specimens). Where practicable, testing the plan might be advantageous (see *Section L3.2. Test Shipments*). A mock or pilot relocation run (*e.g.*, partial movement of the backup systems of freezers and/or liquid nitrogen tanks) in advance of the actual relocation can help to highlight any necessary adjustments. The repository should validate the specimen locations within the storage units post relocation.

***BEST PRACTICE:*** Prior to relocation of a collection to a new legal entity, a transfer agreement should be established and executed with the receiving custodian.

***BEST PRACTICE:*** A map should be created for the new site that will indicate the location of all equipment and specimens that will be transferred.

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

***BEST PRACTICE:*** A comprehensive risk assessment (see *Section B1. Risk Management*) should be undertaken prior to a relocation (including sites and route survey) and should be supplemented by awareness of risk throughout the relocation. Any deviation from the plan should be further risk-assessed and documented before any change takes place.

## G10.2. Logistics for Relocation

### G10.2.1. Storage Units Relocation

Empty storage units sufficient to accommodate the incoming collection may need to be in position in the new location and qualified prior to initiation of the relocation of specimens (see *G10.4. Qualification of Relocated Storage Units*). $LN_2$ storage units may be shipped with the specimen inventory, or separately, depending on logistical benefit. Access to en route $LN_2$ reserves (*e.g.*, on-truck generators) should be assessed. It may not be required when using $LN_2$ shippers that rely on nitrogen for cooling; however, a truck that can hold backup nitrogen may be required for longer transports.

Mechanical freezers (including mechanical automated storage units) generally need to be in position for a minimum period of time prior to use/reuse, which may necessitate the presence of a new freezer or other solution (*e.g.*, a spare or backup unit) for the new location in advance of specimen relocation. Sufficient mechanical freezers to accommodate the incoming specimen batch should be in position in the new location and qualified prior to initiation of the transfer of each specimen batch.

Equipment maintenance professionals should be notified in advance of the relocation date and time to ensure the likelihood of their rapid response in case of equipment failure, particularly when reusing existing storage equipment.


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#### G10.2.2. Specimen Inventory Relocation

Repositories should not unplug and transport equipment storage units containing specimen inventory without first establishing that temperature criteria will be met during transport, even for very short transfer distances. For shipping significant quantities of cryopreserved specimens, large, palletized $LN_2$ dry shippers can be used that can be handled using a pallet-jack or forklift (see *Section H2.1. Liquid Nitrogen Storage Equipment Types*). Specialist logistic providers can provide a service to relocate specimen inventory within shippers or tanks[3]. When shipping specimens in $LN_2$ dry storage/shipper units or other nitrogen devices, consider use of shipper protective containers that meet packaging certification (*e.g.*, ISTA-3A[4]) for the combined shipper and protective container to reduce potential damage to the shipper.

For inventory stored at temperatures in the region of -80 °C, the relocation can be conducted embedded within dry ice or within a refrigerated -80 °C shipping container. Dry ice replenishments should be enabled for longer shipments for inventory transported embedded in dry ice (see *Section L2.2.1. Shipping Temperature*).

The inventory should be secured in place during transit to avoid movement and should additionally be secured against unauthorized access during transit. Authorized access, *e.g.*, for dry ice replenishment, should be enabled. Trained and competent personnel should be present upon receipt of the inventory.

### G10.3. Specimen Integrity during Relocation

Handling during removal from storage, packaging, and relocation will affect the viability of cells/tissues and other types of specimens and may result in degradation of cellular components (see *Section J3.8. Freeze/Thaw and Cooling/Warming Cycles*). It is essential therefore to avoid or restrict cooling/warming cycles when viable specimens are relocated or transferred. The specimens should be maintained within the acceptable temperature range at all stages including while appropriate qualification is performed on the original storage unit(s). For some collections, it may be necessary to preserve the temperature data during transit as part of the specimens' cold chain records.

***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 the cold chain.

***BEST PRACTICE:*** Potential impacts of relocation on specimen quality should be recorded and documented.

### G10.4. Qualification of Relocated Storage Units

Once a storage unit is emptied at the former site, it should be decontaminated as per the repository protocol and freight-shipped to the new site, if required there.

Storage units should be re-qualified after relocation (see *Section D3.6.2.1. Installation, Setup, and Qualification*). The Installation Qualification (IQ) of all types of storage unit should include a thorough inspection for damage due to transport to ensure the storage unit is still suitable for use. Operation Qualification/Performance Qualification (OQ/PQ) should be undertaken as per the OQ/PQ procedure performed when the equipment was originally installed. If separate equipment validation procedures are performed beyond PQ, they may be abbreviated.

Upon completion of qualification, the specimens may be (re)introduced to the qualified storage unit. The process can be repeated for the next consignment of specimens and storage unit(s).

## G11. CRYOSTORAGE

$LN_2$ generates a stable cryogenic temperature environment and is useful for long-term cryostorage. $LN_2$ is consumed during this process and should be regularly replenished to maintain the cold storage capacity. The $LN_2$ supply and storage systems should be scaled to provide sufficient $LN_2$ for normal usage based on known daily $LN_2$ consumption (see *Section H2.2. Monitoring Liquid Nitrogen Storage Parameters*). Critical threshold levels should be defined for establishing the replenishment rate. Replenishment intervals should be scheduled in agreement with the $LN_2$ supplier, based on normal usage. As a guide, the repository should hold a three- to five-day working reserve based on normal rates of consumption. Where possible, an agreement should be established for priority replenishing in the event of emergencies (see *Section B. Risk and Disaster Management*). Both the facility and its personnel should comply with safe working practices for the use of liquid nitrogen (see *Section F4.7. Liquid Nitrogen Safety* and *F4.9. Oxygen Monitoring*). Further information on $LN_2$ storage systems is provided in *Section H. Storage and Processing Equipment* and in the review article by Schiewe *et al*[5].

## G11.1. Liquid Nitrogen Bulk Supply Systems

$LN_2$ bulk storage systems are used to provide a supply of $LN_2$ to static bulk or portable supply tanks. For new or reconfigured facilities, the repository should ensure that the design and installation is carried out by a qualified and experienced provider. To reduce loss of $LN_2$ during movement through the supply piping system, it is recommended to use vacuum-jacketed insulated piping and valves. Such insulation reduces safety risks to personnel by minimizing cold surfaces, condensation, and wet floors. Vacuum levels should be checked on bulk tanks and vacuum-insulated piping per manufacturer recommendations (see *Section H12.1. Equipment Preventative Maintenance and Repair*).

Some organizations produce $LN_2$ in-house (using a $LN_2$ generator) in order to guarantee an autonomous and reliable supply of $LN_2$ (*e.g.*, remote locations, high cost of $LN_2$, other risks). This can have benefits during times of $LN_2$ supply chain disruptions. Maintenance of such complex $LN_2$ generators should be enabled through a professional company (see *Section H12. Equipment Maintenance, Repair, and Replacement*).

Telemetry systems can be used with a bulk storage system to allow both the repository and the supplier to monitor the level of the fluid remotely. The use of a telemetry system enables monitoring of liquid levels in real-time against defined threshold $LN_2$ levels. Noting the frequency and volume of the supply replenishment and within storage tanks can indicate a vacuum issue or leak in the plumbing system or an incorrect setting on the $LN_2$ storage unit.

### G11.1.1. Pressure Relief

$LN_2$ bulk storage and piping systems require pressure relief valves to prevent rupturing of the pipe and tanks in the event of overpressure. Overpressure can be caused by ice buildup on vents. Vents and tanks should be regularly inspected for any ice buildup. Any accumulation of ice should be removed and the cause investigated. A line pressure gauge should be installed to use as an indicator of pressure build events and for troubleshooting longer than normal fill times from the storage system. Where possible, the pressure rating of relief valves should be staggered on the $LN_2$ supply tank, piping, and storage units with the primary relief located outside the building, where practical, and with the lowest pressure located at the bulk tank. Measures should be in place to prevent over-pressurization of the bulk tank during filling (*e.g.*, the bottom tri-cock can be locked off). Internal reliefs can be piped away to external vents and be directed away from personnel and throughways to avoid over-pressure events. An external pneumatic valve connected to the oxygen alarm system and panic buttons should be fitted at the outlet of the bulk tank.

Pressure relief valves should be tested by a professional company according to manufacturer guidelines.

Oxygen sensors and monitoring should be installed by a professional company familiar with $LN_2$ (*e.g.*, a bulk gas supply company) in areas of the facility where $LN_2$ is used (see *Section F4.9. Oxygen Monitoring*). A vacuum-insulated and pneumatically actuated shut-off valve should be located at the bulk tank and linked to the oxygen detection system for immediate termination in the event of oxygen depletion inside the building.

### G11.1.2. Hose Connection

Portable tanks also require the $LN_2$ storage unit transfer hose to be routinely disconnected and reconnected. Special care should be given during this process to avoid introducing moisture, dust, and debris into the supply system and to avoid cross-threading when the hose is reattached. Supply hoses should never be changed when cold (frosted), and the phase separator should be handled carefully to avoid damage.

***BEST PRACTICE:*** Bulk supply tanks, delivered cylinders, and $LN_2$ supply volume and pressure should be verified on a regular basis. All $LN_2$ connections should be routinely checked to ensure they are tight and leak-free.

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# SECTION H: STORAGE AND PROCESSING EQUIPMENT

## H1. GENERAL INTRODUCTION TO STORAGE AND PROCESSING EQUIPMENT

The variety of storage systems available for specimen collections continues to increase as technologies advance. The selection of storage equipment should be based on the following considerations:

- Types and numbers of specimens to be stored (see *Section A3.1.1. Determination of Specimens to be Collected and Storage Environment*).
- Anticipated length of storage time and storage temperature.
- Specimen retrieval frequency and complexity
- Intended use of the specimens (*e.g.*, specimen integrity and fitness for purpose).
- Storage strategies (*e.g.*, use of dual storage units for separation of critical specimens).
- Support systems (*e.g.*, for temperature monitoring and backup).
- Resources available for purchase and operation of equipment (see *Section A3.2.2.1. Identifying and Defining Costs*).
- Size and physical design of the repository, including additional infrastructural requirements.
- Predictions of future growth.

Equipment selection should account for operational specifications and requirements, personnel safety, and interoperability with other systems such as Inventory Management Systems (see *Section I3.7. Interoperability, Portability, and Reconciliation*). Equipment validation, verification, support, and maintenance (see *Sections D3.6. Validation, Verification, and Qualification*, and *H12. Equipment Maintenance, Repair, and Replacement*) should additionally be addressed.

Cold storage in general can be an energy-intensive process. Using energy-efficient equipment can help to minimize both financial costs and environmental impacts. Several manufacturers use compressor systems that are cooled either by water or condensers situated externally to the building so that heat emitted by the equipment does not have to be compensated for by heavy heating, ventilation, and air conditioning (HVAC) requirements. Freezers not using compressor technology (*e.g.*, free-piston or Stirling engine) consume less energy than compressor-based systems, lowering electric utility costs, heat output, and HVAC operational costs. 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 may enable ambient storage for some specimens, eliminating the need for maintaining low-temperature storage environments to ensure specimen integrity (see *H7. Ambient Temperature Storage*)[1]. Repositories in high-humidity areas should employ a dehumidification system to minimize the effects on the storage units (see *Section G3.2. Air Flow, Circulation, and Humidity*). Equipment producing reduced carbon dioxide ($CO_2$) emissions should be considered to reduce environmental impact (see *Section F4.11. Environmental Safety and Sustainability*).

Although adding redundancy increases the cost and complexity of a system design, it may be appropriate when the risk and cost of failure are evaluated.

Everyday equipment operational use should be optimized for cost or energy savings. Savings on operational energy costs can also contribute to reducing $CO_2$ emissions generated by a repository. However, such practices should be carefully evaluated so that they are in line with the intended specimen use, as well as temperature monitoring and alarm response resources.

Provisions for a database to be used for data entry and management and its storage location in the repository should be made. A good system will save time retrieving the requested specimens and associated data and provide critical information for managing specimen inventory (see *Sections I2. Data Management System*, *I3. Inventory Management System,* and *J8. Specimen Inventory Management*).

Temperature mapping for specific storage of temperature-sensitive materials (*e.g.*, within a storage container) should be performed as described in *Section D3.6.2.3. Temperature Verification and Mapping*.

Personal protective equipment appropriate to the task being undertaken should be made available to, and used by personnel; see *Section F3. Personal Protective Equipment*. Additional protective equipment should be used when handling cryogens (see *Section F4.7. Liquid Nitrogen Safety*).

***BEST PRACTICE:*** Critical parameters should be monitored, recorded, and reviewed at regular, defined intervals (*i.e.*, daily, weekly, monthly) to ensure specimen integrity and assess potential equipment failure.

***BEST PRACTICE:*** Repositories should have backup power (see *Section G6. Power*) and/or alternate cooling systems in place, as well as an emergency response plan (see *Section B2.3. Emergency and Disaster Preparedness and Response Planning*).

***BEST PRACTICE:*** The repository should divide the storage of invaluable or irreplaceable specimens between different storage units to reduce the risk of loss. Where feasible, the repository should also enable separate physical locations of those different storage units to avoid catastrophic loss, *e.g.*, due to local facilities damage.

***BEST PRACTICE:*** Storage systems such as walk-in units and automated units should be equipped with redundant compressors that operate under an electrical alternating control system.

## H2. LIQUID NITROGEN STORAGE SYSTEMS

The use of liquid nitrogen ($LN_2$) for long-term specimen preservation is optimal for the storage of many specimen types. 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. This type of cooling has the advantage of being able to maintain the temperature of specimens in the event of a power failure. However, where $LN_2$ supply or access is challenging, associated cost and supply issues should be addressed. Further information on $LN_2$ supply is provided in *Section G11. Cryostorage* and in the review article by Schiewe *et al*[2].

Technological advances have led to the development of systems that facilitate automated or partially-automated handling of specimens during storage in liquid nitrogen vapor phase. Such systems provide areas for handling and retrieval that are cooled to ultra-low temperatures (below -100 °C) and prevent or limit cooling/warming cycles of the specimens.

$LN_2$ can be used for storage in the liquid phase or above the liquid in the vapor phase. Storage in $LN_2$ vapor phase (LNVP) (≤ -150 °C) offers advantages over submersion in the liquid phase (-196 °C). LNVP storage temperatures are sufficient to maintain specimens below the glass transition temperature (*T*g) while avoiding contamination risks and safety hazards inherent in liquid phase storage.

Equipment is also available that allows for $LN_2$ to be used as the coolant for storage temperatures in the +4 to -80 °C range.

A comprehensive assessment of available choices in equipment design should be made prior to making any new purchases.

***BEST PRACTICE:*** The repository should use performance metrics for all $LN_2$ storage units to indicate potential problems and initiate established protocols to transfer specimens to back up units if failure is anticipated.

***BEST PRACTICE:*** Any storage unit used at cryogenic temperatures should be rated for use at these temperatures and have relief valves to evacuate over-pressures (see *Section G11.1.1. Pressure Relief*).

### H2.1. Liquid Nitrogen Storage Equipment Types

$LN_2$-based storage vessels can be divided into two main groups: smaller aluminum cylinders (*e.g.*, Dewars) and larger stainless-steel storage vessels (*i.e.*, cryotanks, freezers). Most are double-walled, vacuum-insulated vessels designed to hold the specimens in racking systems either under $LN_2$ (liquid storage) or in vapor phase above the $LN_2$ (LNVP). These vessels are available in different sizes and specimen capacities, with varying degrees of instrumentation and automation and can be chosen based on the scale of operation within a facility.

#### H2.1.1. Dewars

Aluminum Dewars are efficient, transportable containers that can be situated in readily accessible locations in repositories. If properly vacuumed, Dewars provide a stable storage temperature and low $LN_2$ usage. Originally designed for holding specimens under $LN_2$, some Dewars can also be used for vapor storage by only partially filling with $LN_2$. Although a few auto-fill models exist, the majority require routine manual filling of $LN_2$ to maintain temperature.

#### H2.1.2. Large Storage Vessels

Large storage vessels are designed for medium to long-term storage of specimens. Depending on size, they may fit in a laboratory or require a dedicated room, facility, or repository. Although completely manual units exist, the majority have auto-fill capabilities with instruments for temperature and $LN_2$ level and usage monitoring. These instruments and systems can provide convenience and reliability compared to manual filling, but still require manual verifications at predetermined intervals to ensure specimen integrity. For remote locations, isolated or high elevation facilities, and facilities without vacuum jacketed piping infrastructure, self-sustaining cryotanks can be considered. Reuse of the existing $LN_2$ within the system decreases the dependency for ongoing $LN_2$ supply and for refills.



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Large storage vessels can be categorized as open-top, high-efficiency, and isothermal.

- Open-top storage vessels have a large lid that provides access to an open storage space. Originally designed for $LN_2$ submersion or liquid storage, some models can also be used for vapor-phase storage by only partially filling with $LN_2$ and placing specimens on a platform above the $LN_2$. When converting an existing liquid-only vessel for use with a platform to enable LNVP storage, the repository should be aware that the presence of a vapor-phase platform will reduce the manufacturer-stated capacity of the vessel. Open-top storage vessels are often less expensive but have a higher operating cost and $LN_2$ usage due to the large lid. The opening provided by the larger lid facilitates easier specimen access, especially in a high-throughput workflow. When using open-top storage units for vapor-phase storage, consideration should be given to the storage temperature gradient where upper regions of the vessel can experience higher temperatures, particularly during lid opening. Under these conditions, the temperature can vary significantly depending on the $LN_2$ level; frequency and duration of access; model type; and whether or not a retrofittable, thermally-conductive heat shunt device has been added to the system. This can lead to liquid nitrogen levels below the vapor phase platform reaching critically low levels, or being exhausted, within as little as 24 hours.
- High-efficiency vapor-phase storage vessels have a smaller offset lid for accessing the storage space. This feature provides temperature performance independent of $LN_2$ level and very low $LN_2$ usage with each lid opening. These models, often used in large-scale facilities, are generally equipped with an interior turntable to facilitate access to specimens housed in the inventory system. The turntable is located above the reservoir of $LN_2$ and keeps specimens in the dry storage space. Evaporation of $LN_2$ within the insulated storage vessel provides cryogenic storage temperatures generally between -190 °C at the level of the platform and -170 °C at the vessel lid.
- Isothermal units are triple-walled storage vessels which provide a lower and more consistent storage temperature and smaller vertical temperature range within the storage chamber similar to that for the high-efficiency vapor-phase units. Temperatures at the top of the storage chamber rarely exceed -170 °C. With these units, the $LN_2$ is contained within an additional circumferential wall compartment (rather than underneath the specimens in the specimen storage compartment). $LN_2$ in this jacket extends up to approximately 50% of the unit's height when full. However, such vessels only operate to design specifications when topped up regularly so that there is little change in the $LN_2$ level in the jacket. On auto-fill systems, this means that the $LN_2$ supply line needs to be cooled down more frequently prior to $LN_2$ being delivered into the vessel. This may result in increased $LN_2$ usage. $LN_2$ Dry Storage/Shipper Units are similar to isothermal vessels. These do not have liquid in the specimen storage chamber (*i.e.*, "dry"), reducing the risk of specimen contamination and safety risks associated with $LN_2$ handling while still providing a consistent temperature profile associated with $LN_2$-based storage. These units require priming with $LN_2$ before use and typically stay cold for 10-35 days depending on the model. Commonly used for transporting specimens between locations, they are referred to as dry vapor shippers, shipping Dewars, or cryoshippers. The lack of free $LN_2$ makes these units acceptable for air transportation (see *Section L2. Transport Specifications*).

Use of aluminum storage racks within storage vessels can reduce the temperature differential between the bottom and the top of the vessel's storage compartment. Where $LN_2$ refrigeration is used, an adequate supply of $LN_2$ should be maintained. This amount should be determined based on critical threshold levels and availability of re-supply (see *Section G11. Cryostorage*). Bulk supplies should be routinely monitored at least weekly. A telemetry system can be installed (see *Section G11.1. Liquid Nitrogen Bulk Supply Systems*).

***BEST PRACTICE:*** All $LN_2$ and LNVP storage vessels (including cryoshippers) should undergo routine maintenance (including cleaning, temperature mapping, and calibration of the vessel's controls and monitoring sensors, and periodic vacuum testing/renewal, *e.g.*, by hold-time testing, where practicable). Vessels with a compromised vacuum should be repaired when possible and re-evacuated or discarded.

### H2.2. Monitoring Liquid Nitrogen Storage Parameters

Routine monitoring (daily/weekly) of $LN_2$ storage vessels should be carried out once the bulk $LN_2$ storage system has been installed (see *Section G11.1. Liquid Nitrogen Bulk Supply Systems*) and the units have undergone validation and verification (see *Section D3.6. Validation, Verification, and Qualification*). Any inventory racking system should be installed prior to validation. Manufacturer's recommendations for installation and operation should be followed. Following successful validation, the $LN_2$ storage vessel should be re-filled with $LN_2$ as per manufacturer recommendations and the temperature allowed to stabilize for 24-48 hours prior to introducing specimens.

The critical parameters for $LN_2$ storage are $LN_2$ level, daily $LN_2$ consumption rate, and storage temperature. $LN_2$ level and consumption are interrelated since the difference in pre- and post-fill levels can be used to calculate the amount of $LN_2$ consumed. Both are related to the ability of the vessel to maintain a stable storage temperature, for preservation of specimen integrity.

Most larger vessels are provided with automated monitoring systems designed to record these parameters and alarm if parameters exceed user defined specifications. Such alarm outputs should be connected to facility-wide monitoring systems to enable remote monitoring. Even where automatic monitoring and recording are in place, repositories should also manually record critical parameters on a daily or weekly basis. Smaller units such as Dewars typically lack monitoring and $LN_2$ level control options, thus requiring a higher level of management and monitoring. Add-on accessories for temperature and $LN_2$ level monitoring are available, and wireless-remote, weight-based monitoring systems can provide continuous measurements that can be precisely correlated to $LN_2$ levels and used to determine evaporation rates. If a secondary system for monitoring temperature and/or $LN_2$ level is used, it should be installed, calibrated, and verified prior to storing any specimens. Alarms and alerts generated by the system should be tested and verified. This includes local audio-visual alarms and connections to secondary or remote monitoring systems.

Most monitoring is performed using manual methods. Measuring $LN_2$ levels manually requires the use of a temperature-tolerant plastic or metal measuring stick (dipstick) calibrated in metric or imperial units. These are available from manufacturers or suppliers and are often provided with the storage unit. Other devices of various materials may be used but should be evaluated for their ability to withstand cryogenic temperatures. A hollow tube should never be used as $LN_2$ will rapidly shoot out of the top as it is inserted into the cold $LN_2$ with the associated hazards (see *Section F4.7. Liquid Nitrogen Safety*). A separate dipstick should be used for each storage vessel to avoid potential cross-contamination between units. It is recommended to clean and disinfect dipsticks, *e.g.*, using ethanol alcohol-moistened lint-free tissue paper prior to use. UV sterilization of dipsticks contributes to a further decrease of the risk of pathogen-related contamination.

For manually filled $LN_2$ storage units, the $LN_2$ level should be monitored and recorded before and after filling. Since auto-fill units are often programed to fill as needed, it is difficult to manually monitor $LN_2$ levels accurately and thereby determine $LN_2$ usage. Here, an electronic monitoring system is the best source for tracking and recording $LN_2$ consumption. Where auto-fill units are programmed to fill at set times, manual monitoring can be carried out before and after the fill. In either case, the post-fill level measurement allows for the calculation of $LN_2$ consumption and determination of storage unit evaporation rates. An alternative method is to take the current $LN_2$ level and subtract that from the previously recorded post-fill $LN_2$ level. If performed daily, this will allow calculation of consumption rates for a specific storage vessel that can be averaged out with standard deviations. Monitoring $LN_2$ consumption through measurement of $LN_2$ levels should include comparison against a clear, acceptable range of consumption based on manufacturer's guidelines and in accordance with the repository's average usage values for each $LN_2$ storage vessel. An increased $LN_2$ consumption rate, beyond manufacturer guidelines and/or the standard consumption rate, for any $LN_2$ storage vessel is a critical sign of potential, imminent equipment failure and action should be taken immediately to investigate the cause of the increased consumption.

All $LN_2$ storage vessels should be equipped with continuous temperature monitoring as temperatures within the unit will change depending on the level of $LN_2$ within the vessel and during normal operation. Even when specimens are completely submerged in $LN_2$, temperature monitoring and the associated cold chain records can provide reassurance that specimens are maintained at a proper temperature if and when the $LN_2$ level falls out of range. An acceptable temperature range, based on the type of specimens being stored and their intended purpose, should be predefined by the repository (*Section J3.5. Specimen Temperature*). Upper and lower temperature limits should be set. In LNVP vessels, exceeding the lower limit can be indicative of $LN_2$ ingress above the vapor-phase platform, while exceeding upper limits may indicate incomplete replenishment of $LN_2$ during filling.

$LN_2$ storage vessels equipped with electronic monitoring should have built-in height-adjustable temperature probes. These should be positioned at the lowest and highest points of specimen storage (*i.e.*, level with the bottom and top of any specimen inventory system). For small $LN_2$ storage units lacking built-in temperature measurement, or where a separate temperature sensor is necessary for alarm/monitoring purposes, an independent temperature probe or probes should be installed at or above the highest level of the stored specimens. As with $LN_2$ consumption, a clear acceptable temperature range should be defined (with standard deviation where multiple probes are positioned at the same height).

All temperature sensors should be calibrated at installation and then regularly as part of planned preventative maintenance (see *Section D3.6.2.2. Calibration*). Calibration should be against a currently certificated thermometer traceable to national standards.

Units should undergo re-validation if significant changes are made to automated systems or software that might detrimentally impact monitoring and alarm systems.



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***BEST PRACTICE:*** In repositories where specimens are stored in LNVP, personnel should regularly use a technique whereby physical measurement of the liquid nitrogen level is taken with a tool such as a dipstick to confirm the liquid nitrogen level. These readings should be recorded.

***BEST PRACTICE:*** Where $LN_2$ refrigeration is used, appropriate $LN_2$ level, $LN_2$ fill activity, and temperature monitoring equipment as well as manual monitoring should be utilized for storage.

### H2.3. Detecting Liquid Nitrogen Storage Equipment Failure

Storage vessel failure can lead to a potential loss of specimen integrity. Signs of impending failure can include elevated storage temperatures, increased $LN_2$ consumption, and/or abnormal visual observations:

- Temperature monitoring may indicate that $LN_2$ level is low and/or equipment is not functioning properly. However, an out-of-range temperature alert is sometimes the last indication of equipment failure as a $LN_2$ supply alarm is typically activated prior to this.
- Increased $LN_2$ consumption is often an indicator of a slow leak that may result in unit failure over time. It may also reflect a more imminent problem.
- Changes to the visual appearance of a storage unit that are inconsistent with the way the storage unit normally looks, such as dents or warping, may indicate potential equipment failure. Both the outside and, where possible, the inside of the unit should be checked regularly. Condensation or ice on the outside of the storage unit or bulk $LN_2$ storage and piping systems (see *Section G11.1.1. Pressure Relief*) may indicate a vacuum leak. Routine visual inspection can, over time, help to differentiate observations due to regular activity and those associated with abnormalities. For example, frost associated with $LN_2$ filling vs. permanent ice spots that may indicate a hot spot caused by damage to a seal, degradation to vacuum insulation[3], or a faulty lid.

Routine monitoring (daily/weekly), recording, and review of these parameters allows early detection of abnormal trends that may indicate equipment failure. Any out-of-specification event should be investigated in a timely manner and response times to an abnormal increase in temperature, especially if this triggers an out-of-specification alarm, should be as rapid as possible. Records of manual verifications should be retained and referenced to observe any developing trends or changes in system performance and made available for audits.

Where a storage unit is suspected of or is failing, personnel should transfer the specimens to a back-up storage unit as fast as possible, subject to observing all personal safety requirements (see *H9. Backup Storage Capacity* and *Section F4.7. Liquid Nitrogen Safety*). $LN_2$ levels should be maintained in the failing unit, as lowering levels during a failure may result in the implosion of the interior wall, preventing the transfer of the stored specimens.

***BEST PRACTICE:*** A repository should use a communication interface for remote transmission of data to the controllers of $LN_2$ freezers to facilitate remote shutoff of the $LN_2$ supply in case of emergency, fill level sensor failure, or solenoid failure (see *Section I3.13. Data Security for Inventory Systems*).

## H3. MECHANICAL FREEZERS

Mechanical freezers are used for a variety of storage temperature ranges and come in a wide variety of sizes, configurations, and electric voltages. As these devices are generally connected to commercial power systems, backup power should be (automatically) activated for critical units in the event of a commercial power failure (see *Section G6.1. Backup Power Supply*). An emergency response plan detailing the backup, notification of personnel, and response should be implemented and tested periodically (see *Section B2.3. Emergency and Disaster Preparedness and Response Planning*). The length of time that results in significant warming of stored material varies according to the properties of the stored specimens, temperature throughout the freezer, ambient conditions, and design and maintenance of the unit. Chest systems retain cold better upon door opening than upright units, whereas uprights typically provide more efficient compartmentalized storage. Frost-free freezers with daily heating cycle built into the doors should not be used for repository storage, due to gradual deterioration/desiccation of specimens stored near the doors and walls of the unit. 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 extended power loss. Any freezer implementing this type of emergency backup cooling system should be specifically designed to accommodate coolants used, and adequate supplies of refrigerant gas should be kept on hand at all times to operate the system. Safety precautions should be taken to maintain the health and safety of personnel in areas where compressed gasses such as $CO_2$ or $LN_2$ are used (see *Sections F4.2.2. Compressed Gasses*, *F4.7. Liquid Nitrogen Safety*, and *F4.9. Oxygen Monitoring*)[4].

Inadequate air circulation may lead to mold growth and other harmful microbial contamination situations. HVAC systems are more efficient than simple ventilation systems at maintaining temperatures and humidity (see *Section G3.2. Air Flow, Circulation, and Humidity*). Ensure that mechanical storage units are not placed under or around any HVAC vents or windows that may submit the unit to direct airflow or sunlight. Independent of backup cooling solutions, efforts should be made to ensure that freezers and refrigerators are positioned in repositories to allow adequate airflow. Insufficient distance between units or between units and walls may lead to overheating of compressors, shortening compressor life. While manufacturers guidance should be followed, most ULT freezers require at least 6-8 inches (15-20 cm) of space on the sides/top/rear of the unit for heat dissipation. Providing up to 13 inches (33 cm), particularly in a restricted room, can further improve compressor operation as evidenced by fewer oscillations after door opening to regain the set temperature range. In addition, ease of access behind mechanical freezers enables regular maintenance. Sufficient space should also be provided for the incidental tools and instruments (*e.g.*, carts) used to perform large-scale critical activities at the face of the freezer, including specimen inventory auditing, specimen retrieval, and emergency specimen transfer.

Extension cords should be avoided for provision of power to mechanical freezers. Each freezer should be plugged into its own electrical outlet and circuit capacity should be accounted for. If access to the plug outlet is restricted during operation, a nearby isolator should be accessible to cut power to the freezer in event of an emergency (*e.g.*, freezer fire). To prevent accidental unplugging, a mechanical freezer can be electrically fixed in place or directly connected to the power source, eliminating the need for a plug and separate outlet. The repository should consult professional electrical expertise where required.

A cascade freezer system comprises a series of storage units connected to a central cooling unit. The benefit of cascade systems is greater storage capacity in a smaller footprint with significantly reduced energy consumption compared to stand-alone units. In addition, mechanical cooling systems may be placed in areas external to the specimen storage reducing heat and noise in the storage/work area. The upfront cost is typically greater than that of stand-alone units; however, the reduced footprint and energy consumption can compensate 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 fully redundant cooling systems to mitigate failure and allow for maintenance of the system 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 10 storage units with 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 assure the critical temperature ranges during access of the individual units and response times to alarms.

### H3.1. Monitoring Mechanical Storage Parameters

Routine monitoring (daily/weekly) of temperature and ice buildup in mechanical freezer units should be carried out once properly installed and the units have undergone validation and verification (see *Section D3.6. Validation, Verification, and Qualification*). Any proposed inventory shelving and/or racking systems should be installed prior to validation. Manufacturer's recommendations for installation and operation should be followed.

Many laboratory-grade mechanical freezers are provided with automated monitoring systems designed to record temperature and provide alarms if this parameter exceeds user defined specifications. Where possible, such alarm outputs should be connected to facility-wide monitoring systems to enable remote monitoring. Even where automatic monitoring and recording is in place, repositories should also manually record temperatures on a daily or weekly basis or as a result of frequent door opening. Add-on accessories for temperature monitoring are available, and wireless-remote systems can provide continuous temperature monitoring. If a secondary system for monitoring temperature is used, it should be installed, calibrated, and verified prior to storing any specimens. Alarms and alerts generated by the system should be tested and verified. This includes local audio-visual alarms and connections to secondary or remote monitoring systems. Consideration of placement of independent temperature monitoring probes based on results of initial temperature mapping is advised, *e.g.*, probes should be placed in predetermined warmer or variable temperature areas in the chamber (see *Section D3.6.2.3. Temperature Verification and Mapping*).

An acceptable temperature range, based on the type of specimens being stored and their intended purpose, should be predefined by the repository and/or end-users (see *Section J3.5. Specimen Temperature*). The facility operator is responsible for setting and enforcing: 1. the critical limits (temperatures and time) and 2. the response times to alarms. Use of a higher set temperature to save energy may not be recommended based on the need to fulfill specimen fitness for purpose.

It is important to consider the layout of the shelving system to maximize the available space, including dimensions of the shelving units, the dimensions of the items to be stored, and any specific requirements for easy accessibility and for rapid


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specimen transfer between mechanical freezers during emergencies. Both the empty space with freezer chambers and door openings should be minimized to retain cold air within the unit. Door-opening frequency and the length of time the door is open should be minimized and the details can be recorded for alignment with monitored temperature profiles for reporting on specimen cold chain.

All temperature sensors should be calibrated at installation and then regularly as part of planned preventative maintenance (see *Section D3.6.2.2. Calibration*). Calibration should be against a currently certificated thermometer traceable to national standards.

Frost and ice can form in between the door gasket and frame to form an air gap, which can decrease the refrigeration effect of the unit. Excess humidity in areas where mechanical freezers are used can increase ice buildup. This may also be true of pressure relief ports. This should be monitored, and ice buildup can be removed with care between defrosting cycles, as necessary. Plastic scrapers are generally provided with units for routine scraping of the doors. Follow specific device instructions for this to avoid damaging the unit.

Mechanical freezers should undergo re-validation if significant changes are made that might detrimentally impact specimen integrity, operation, or monitoring and alarm systems.

### H3.2. Detecting Mechanical Freezer Storage Equipment Failure

Mechanical freezer failure can lead to a potential loss of specimen integrity. Signs of impending failure can include elevated storage temperatures or increased noise of operation to maintain temperature.

To enable early detection of abnormal trends that may indicate equipment failure, the repository should perform:

- Routine temperature monitoring (daily/weekly), recording, and review. This can include regular comparisons of probe monitoring temperature with the freezer display temperatures. Any unanticipated discrepancy (*e.g.*, not due to normal door-opening activities to access specimens) should be further investigated and monitored to determine the potential for an out-of-specification event.
- Routine inspection for ice build-up, frayed cables, cracked plugs, and/or the appearance of abnormal operation (*e.g.*, excessive noise or leaking). Personnel using freezers should be trained to observe and report potential signs that may result in failure.

Any out-of-specification event should be investigated in a timely manner and response times to an abnormal increase in temperature, especially if this triggers an out-of-specification alarm, should be as rapid as possible.

Records of manual verifications should be retained and referenced to observe any developing trends or changes in system performance and made available for audits.

Where a storage unit is suspected of or is failing, personnel should transfer the specimens to a functioning back-up storage unit within the acceptable temperature range as fast as possible, subject to observing all personal safety requirements (see *H9. Backup Storage Capacity* and *Section F4.5. Physical Safety*).

## H4. AUTOMATED STORAGE SYSTEMS

Automated specimen storage and retrieval systems keep specimens at their required storage temperature while minimizing temperature fluctuations. Some cold storage units (freezers, refrigerators) enable automated specimen entry and retrieval. This may reduce dependency on personnel for such activities, improve metrics for access to specimens, and may help maintain specimen quality more effectively as warming events of specimens can be avoided. Where temperature can impact specimen integrity, it is important for the specimen storage temperature and the specimen retrieving temperature to be as close as possible to prevent warming events. Repositories should be aware of any possible implications for specimen integrity, *e.g.*, associated with holding retrieved specimens at higher temperatures, *e.g.*, -20 °C, than a specified storage temperature range, *e.g.*, -65 °C to -80 °C, for long periods of time, prior to distribution. Where this is a feature, procedures should be in place to lessen the impact on the integrity of the specimens. Other considerations for the use of automated specimen storage are specimen tracking capability, audit trail, maximization of the storage capacity, and data management (see *Section I3.16. Data in Automation*). An important consideration is the choice of specimen storage container (see *Section J3.1.5. Specimen Identifiers/Labels and Automation*). Most systems can consolidate empty positions of stored racks (see *Section J8. Specimen Inventory Management*). 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 of specimens. Many systems can be expanded as the

collection grows. Most automated systems have lower energy requirements, smaller footprints, and require lower HVAC output than individual storage units[5,6]. However, the process of procurement, installation and setup can be extensive, requiring significant repository resources including budget, personnel time and expertise for optimization of repository storage and retrieval operations[7].

***BEST PRACTICE:*** A repository should carefully evaluate the criteria for repository resources (*e.g.*, space, personnel expertise, suitability of specimen containers and specimen identifiers, and costs [both initial and ongoing maintenance and other servicing costs]) prior to purchasing an automated storage system.

## H5. 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 and benefit from temperature monitoring, recording, and alarm alert response systems.

## H6. WALK-IN ENVIRONMENTAL STORAGE SYSTEMS

Walk-in refrigerators, cold rooms, 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 (see *Section F3. Personal Protective Equipment*). 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. The repository should additionally review any health and safety implications for personnel using walk-in storage systems (see *Section F4.5.2. Safety in Walk-in Units*).

Temperature mapping of facility cold rooms should be undertaken as part of the commissioning by the manufacturer or supplier. This should be repeated periodically but can be expensive and may require competent external contractors to complete. The World Health Organization UNICEF Hub has produced an evidence brief of examples of temperature mapping conducted in an existing cold room to control compliance, and identify and address performance gaps[8]. See *Section D3.6.2.3. Temperature Verification and Mapping* for temperature mapping in equipment.

***BEST PRACTICE:*** To inhibit the rusting of metal parts of walk-in storage systems, repositories should apply anti-rust coatings and install dehumidification systems.

## H7. AMBIENT TEMPERATURE STORAGE

While formalin-fixed, paraffin-embedded (FFPE) tissues (see *Section J3.7.1. Preservation Techniques*) have been stored at room temperature for over a century, 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 DNA and RNA[1], 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[9]. Prior to implementation, all matrices should be evaluated to be sure that they are appropriate for downstream purposes and applications (see *Section D3.6. Validation, Verification, and Qualification*).

### H7.1. Humidity Monitoring

Humidity can impact on ambient temperature storage affecting specimen stability. The humidity level can change rapidly in some regions due to changes in the environmental control of the facility or seasonal changes (see *Section G3.2. Air Flow, Circulation, and Humidity*). A significant increase in humidity level can challenge the safety conditions for the personnel working with specimens. Where humidity is an issue, sensors should be located in different areas of the storage room


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and dehumidification strategies employed. This may include use of a portable dehumidifier. In some circumstances, an industrial dehumidifier may be required to control excess humidity constantly.

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. Choosing appropriate, moisture-resistant containers or utilizing moisture barriers can help mitigate risks.

### H7.2. Storage of FFPE Tissue Blocks and Slides

Formalin-fixed paraffin-embedded (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 chronological 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. Vacuum-packing with desiccant may reduce the impact of ambient hydration, protecting specimen integrity[10] (see *Section J3. Specimen Integrity*).

Manual handling of FFPE specimens is associated with major drawbacks, including: (1) ambiguous hand labeling leading to misidentification; (2) returning a specimen to a different storage location leading to an inability to relocate the specimen; and (3) difficulty in controlling incoming and outgoing specimens, which may result in challenges in management of the specimen inventory (see *Section J8. Specimen Inventory Management*).

New technologies for automating FFPE storage are being developed. Semi-automated systems using barcoded blocks and slides (2D barcodes are preferred; see *H4. Automated Storage Systems*) not only reduce the workload 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 optimally maintained when the FFPE blocks are stored at -20°C to 4°C. Repositories should validate the fitness for purpose of the paraffin used to sub-zero temperatures.

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

## H8. CONTAMINATION ISSUES

Every effort should be made to avoid contamination of specimens (see *Sections G9. Pest and Contamination Control* and *F4.1. Biorisk Management*). 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 and cardboard boxes) that can facilitate fungal growth. Within storage containers, broken vials or straws may release their contents, which could contaminate other specimens. Personnel should be aware of the potential for pathogen contamination of specimen containers when submerging in non-sterile $LN_2$ (see *Section F4.1.1. Biosafety*). Periodic monitoring should be encouraged to visually monitor for all contamination and for items that may be inappropriately stored. Repositories should consider the use of dehumidification systems (see *H7.1. Humidity Monitoring*).

***BEST PRACTICE:*** To prepare for the possibility of storage and processing equipment contamination, decontamination strategies (including equipment and procedures) should be in place.

## H9. BACKUP STORAGE CAPACITY

Adequate backup capacity for low-temperature units should be maintained in anticipation of possible equipment failure (see *Section B2.3. Emergency and Disaster Preparedness and Response Planning*). If space and funds allow, backup storage for each storage condition should be available within the repository. The proximity of the backup capacity should enable safe and efficient specimen transfer, keeping in mind cold chain management (see *Section J3.5. Specimen Temperature*) and personnel welfare (see *Section F. Health and Safety*). Where this is not possible, repository personnel 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. Backup power should also be available (see *Section G6. Power*).

The requirements for backup storage capacity can be optimized by choosing a modular system of operation, *e.g.*, through the use of internal racking in mechanical freezers that enables bulk movement of boxed specimens. Internal racking that fits neatly within all models of freezer types used reduces the need to have specific backup units for particular freezer models.

***BEST PRACTICE:*** An empty back-up storage unit or unit(s) should be available at any time for contingencies (*e.g.*, emergency relocation of specimens). The extra-capacity equipment should be equal to the capacity of the largest single storage unit and should be maintained in reserve within an acceptable buffer of the specified temperature range. 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 or where necessary. The storage unit name or number(s) as well as the location(s) within the unit to where the specimens have been relocated should be documented.

## H10. 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 should account for normal operating variations and some acceptable variation for warming when specimens are 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 personnel, an automatic temperature-monitoring system should continually monitor temperatures of all critical equipment and other important parameters, create logs, generate audit trails, and generate 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 repository should be aware of the possibility of measurement drift or thermocouple probe failure over time. Such automatic temperature monitoring systems should be appropriately calibrated (*i.e.*, using a reference thermocouple calibrated for the temperature storage conditions) and verified on a periodic basis (*e.g.*, using storage unit temperature display) to maintain confidence in measurement accuracy (see *Section D3.6. Validation, Verification and Qualification*).

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 personnel; see *Section G7. Security and Access*).

Depending on the size of the repository and personnel availability, more than one individual should be available to respond to an alarm raised where possible, in case the first individual cannot receive or respond to the notification. For instance, the repository might use an alarm-alert system that enables a cascade of alerts for additional responders. Such cascade alerts should be auditable. Alarm conditions should be responded to in a timeframe that minimizes the likelihood of damage to the stored specimens. Repository management should ensure that trained response personnel who are deemed competent and can take corrective action are available or reachable 24 hours per day, seven days per week (see *Section E. Training and Competency*).

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. In addition to monitoring 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 repository need (see *Section D3.6.2. Instruments and Equipment*).



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***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 personnel 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 enables personnel to proactively evaluate each unit's performance and determine if any maintenance work is needed.

## H11. 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 (see *Section D3.6. Validation, Verification, and Qualification*). Methods used to calibrate for accuracy and precision of the pipetting process include gravimetric and spectrographic techniques. These procedures should be performed 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), nucleic acid extraction, aliquoting, DNA normalization, etc. Additional hardware options such as cooled plates, shakers, heaters, and incubators can be included. These robotic systems utilize disposable tips. Filter tips can be used to prevent cross contamination of specimens.

Additional automated processing systems which can help assist laboratories in the performance of their daily operations include automated weighing stations, tube sorters, cappers and de-cappers, and detection systems for quantification. As with any automated specimen processing system, a validated system should be employed to track and register all specimens being processed (see *Section I3.16. Data in Automation*). See *Section J3.1.5. Specimen Identifiers/Labels and Automation* for information on specimen identification to ensure compatibility with automation.

## H12.EQUIPMENT MAINTENANCE, REPAIR, AND REPLACEMENT

A system for preventative maintenance and repair of storage equipment, supporting systems, and facilities should be in place. Such maintenance should include calibration and verification (see *Section D3.6. Validation and Verification, and Qualification*, including *D3.6.2.2. Calibration*) as these can be a source of non-compliance in audits (see *Section D3.7. Auditing for Performance Review*). Equipment exposed to (potentially) infectious materials should be properly disinfected. The choice of disinfectant to be used depends on the situation and other factors (see *Sections F4.1.1. Biosafety* and *C1.5. Environmental Impact and Biobanking*). Some disinfectants are broad spectrum (effective against 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.

### H12.1. Equipment Preventative Maintenance and Repair

Essentially all equipment composed of multiple components wears out with time, use, and exposure to various environmental conditions. System maintenance should be performed at regular, established intervals (daily, weekly, monthly, etc.) as per manufacturer recommendations and as determined as fit-for-purpose aligned with repository practices. Performing routine maintenance and optimizing equipment parameters within manufacturer specifications may significantly extend the lifetime for equipment used. For mechanical freezers, this may include a periodic changing out of fluids, cleaning of filters, calibration of probes, and removing ice from the tops and sides of the interior chambers and rubber gaskets. Routine maintenance also extends to batteries within battery operated systems (*e.g.*, emergency lighting and uninterruptible power supply; see *Section G6.1.1. Uninterruptible Power Supply*).

It is important to communicate with manufacturers and service providers regarding the importance of the specimens being processed and stored as well as the surrounding workflows so they can help develop appropriate verification and maintenance schedules. Repositories should consider what routine maintenance is recommended by the manufacturer before equipment is procured and put into service to ensure that specimen integrity is not affected, *e.g.*, freezers with automatic defrost or frost removal may be problematic (see *H3. Mechanical Freezers*).

The repository should establish annual maintenance contract(s) based on the repository critical equipment list and contracted company's area of expertise.

The repository should have a documented list of all the equipment it owns and/or uses (*i.e.*, equipment inventory), and all newly received equipment should be recorded within this list at the time of delivery. 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 known, the date(s) of incident(s), and the non-conformity compared to required standards and manufacturer recommendations (see *Section D3.8.1. Non-Conformities*). Where an incident (*e.g.*, equipment malfunction or breakdown) has a potential detrimental effect on the quality of specimens and data, the equipment should be removed from use and the non-conformity managed (see *Section D3.8. Quality Improvement*). Equipment taken out of use should be labeled appropriately to prevent use, and the event recorded, including a record of the date when returned to service, if applicable. Repaired equipment should be re-validated and re-verified prior to resumption of use (see *Section D3.6. Validation, Verification, and Qualification*).

***BEST PRACTICE:*** For critical equipment, the repository should have a plan for obtaining or holding key spare parts according to resources and availability of supply.

***BEST PRACTICE:*** Routine maintenance should be performed at regular, established intervals per manufacturer recommendations and as determined as fit for purpose aligned with the repository's practices.

***BEST PRACTICE:*** Annual maintenance, servicing, or repair should be performed by factory-trained and/or certified technicians.

***BEST PRACTICE:*** Maintenance logs should be stored (physically or electronically), in a secure location, with any changes recorded and older versions retained.

### H12.2. Repair or 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 spare 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 5-12 years, but actual lifetimes can be shorter or longer. Liquid nitrogen freezers may have lifetimes extending from 10 to 35 years.

Long-range plans should be made to address the possible repair and replacement of equipment critical to the functioning of the repository. Decisions to repair or replace may be influenced by:

- Safety concerns due to malfunctioning of failing units.
- Integrity concerns for critical specimen or data.
- Parts that are difficult or costly to find and replace.
- Improved energy efficiency and lower environmental footprint with newer models.
- Frequency and cost of repair versus replace.
- Recommendations based upon received experience on the expected lifespan of alternative models.

Since replacing cold storage units and processing equipment can be expensive, it is recommended to anticipate these expenditures and have some financial reserves available to address this when decisions to replace equipment are made (see *Section A3.2.2.1. Identifying and Defining costs*). If multiple pieces of the same equipment type need replacement at one time, it might be beneficial to use interim equipment or backup equipment while gradually introducing the new equipment over time. This allows for a progressive introduction of new equipment while staggering any repair and replacement schedules. Attention should be given to the expected lifespan of the equipment; for instance, prior experience with the equipment may inform mean time between failures.

Equipment being replaced should be decommissioned according to a repository or organizational policy that accounts for health and safety, environmental impact, recovery, and careful destruction of any sensitive information or data (see *Section I2.3.1. Data Security*) and waste disposal regulations. Repositories can avail of trade-in or buyback programs or both, where practicable.



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***BEST PRACTICE:*** Repositories should plan for the orderly replacement of equipment.

***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 also fulfills the criteria for that equipment.

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# SECTION I: INFORMATION MANAGEMENT

## I1. GENERAL INTRODUCTION TO INFORMATION MANAGEMENT

Data associated with specimens is of utmost importance for effective scientific research and reproducibility. Extensive and accurate data associated with specimens is a fundamental asset to each repository. In addition, today's repositories are growing more dependent on data, and in tandem, on supporting data systems. These are key to a variety of functions including general operations, specimen management, communications, stakeholder relations, image or specimen analysis, shipping and logistics, automation, among many others.

Not only are specimen data collected or acquired, but other data are generated by a repository. Data not associated with specimens are often an untapped resource of use to the repository to optimize operations, as well as to other stakeholders, and can be termed repository operation data. Such data are extremely wide ranging and can include agreements with stakeholders, key performance metrics, and specimen location data, among many others.

Data that are specifically generated and used in managing operations can have various levels of sensitivity or confidentiality concerns. While sensitive data are most often associated with participant or donor information, other examples include proprietary processes, intellectual property information, personnel and end-user information, and finances. Therefore, it is critical to understand what data are collected, acquired, and/or generated during the different phases of the repository, both intended and unintended, and how to sufficiently protect and leverage these resources.

Fit for purpose (FFP) data should be aligned with the quality goals of FFP specimens (see *Section D1. General Introduction to Quality Management*), to underpin data that are appropriate for the intended use by the end-user. FFP data collection, distribution, and use should conform to relevant regulations, including those pertaining to regions to which the specimens and/or data may be distributed or used (see *Section C1.2. Legal Implications*). This often necessitates balancing adherence to stringent data regulations (*e.g.*, by using techniques such as data minimization) with the goal of data interoperability (see *I3.7. Interoperability, Portability, and Reconciliation*) and sharing (see *I3.5. Virtual Platforms*).

## I2. DATA MANAGEMENT

Effective information or data management (the terms *data* and *information* are used interchangeably herein) is key to ensuring financial, social, and operational sustainability, quality, value, interoperability, compliance with regulations, risk reduction, and growth potential. Central to data management are the considerations of the types of data that may be used or generated; the hardware and software systems used for processing, storage and retrieval; and the protocols and permissions used to access or manipulate the data. Data may be processed, stored, and accessed in a variety of formats, from paper formats or simple spreadsheets to complex networks or cloud services, making it challenging to track, manage, and validate. Therefore, it is important to understand that data management includes planning, generating, transforming, and verifying data during the data lifecycle (see Figure I1. Mapping Repository Data Flow and Management). This section addresses data management recommendations that are applicable to all data and data systems used in a repository. Specific recommendations on inventory management systems (IMS) to manage specimens and specimen-associated data, are provided in *I3. Inventory Management System*.



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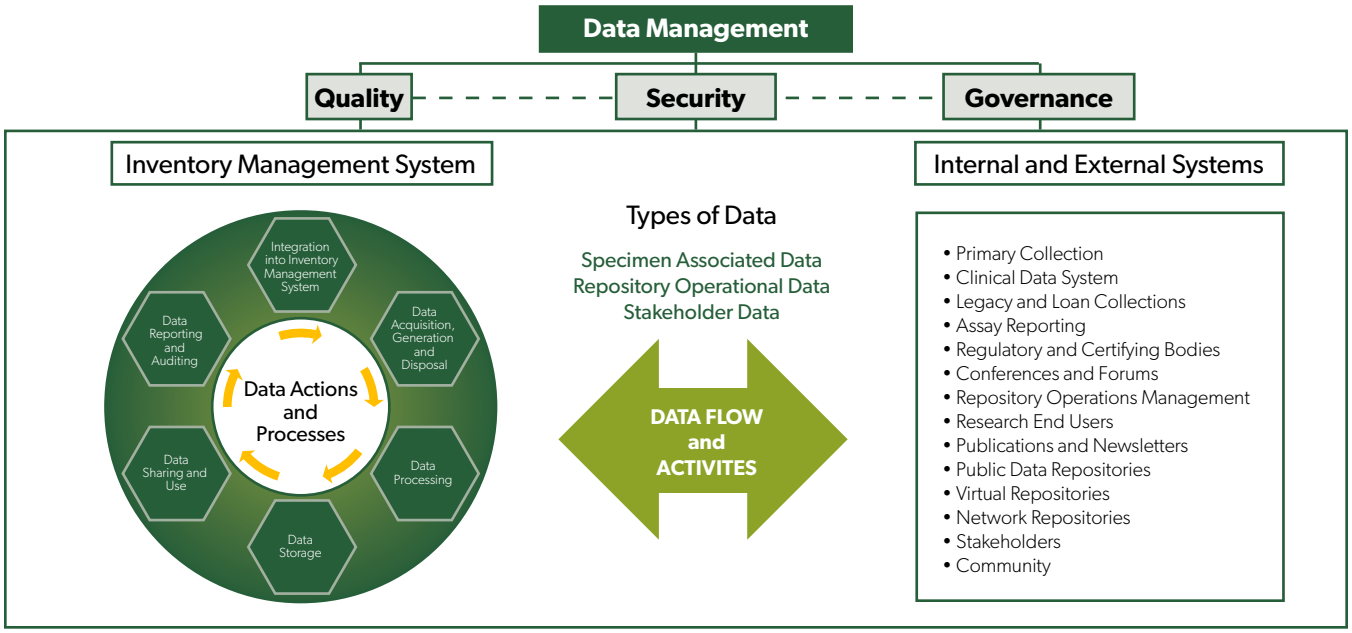


**Figure I1.** Mapping Repository Data Flow and Management. Due to growing use of data, automation, and computer systems, as well as stringent data regulations, repositories should fully understand the life cycle of the data and its impact. This schematic highlights the possible data flow relevant to a repository with data management being the foundation to ensure data security, quality, and governance.
The blue ring shows typical data processes, primarily conducted and maintained within the IMS.

The green bidirectional arrow displays potential data that can be transmitted between the IMS and other data systems, platforms, or networks. These internal and external systems may be physically separate either in terms of the data systems, and/or the physical location of the corresponding organization. To achieve secure, accurate, and reliable data processing and transmission within and between systems, careful planning and governance oversight is recommended for maximal data interoperability, management, quality assurance, and security, including protection of sensitive and private information.

## I2.1. Data Management Plan

A data management plan (DMP) is a formal document that is part of the repository business and/or operational plan (see *Section A4.4. Operations Plans*). A DMP should outline what is needed to collect, generate, process, analyze, manage, share, and preserve data associated with specimens, participants/donors (including patients, communities, etc.), and operations. The DMP can be in electronic or paper form and describes the sources of data, types of data collected, how it is organized (whether local or linked) and stored, what formats are accepted and controlled, and how and what data will be made accessible. The DMP can revolve around computer- or paper-based data management systems (or hybrid of the two). If computer-based, the term data management system (DMS) refers to the software and hardware systems used to manage databases at the repository. The DMP should indicate how users are trained and deemed competent (see *Section E2. Training Structure*) in the organization's security and privacy guidelines and SOPs to ensure the integrity of access control. The DMP is a high-level document, with details of how data are handled specifically addressed in the repository's standard operating procedures (SOPs) and the quality manual (see *Section D3.1. Quality Manual*).

Key elements of a DMP address the following:

- Data governance outlining custodianship of data, role-based responsibilities, and levels of access, including for data sharing (see *Section K2.1.1. Data and ELSI Governance in Access, Use, and Distribution*).
- Data and systems evaluation using appropriate instruments or practices.
- Data provenance, ensuring traceability and tracking of data.
- Data security measures, access controls, risk management, and protection of sensitive and/or private data.
- Environmental sustainability of data and digital infrastructure (see *Section A3.2.1. Repository Sustainability*).
- Policies on sharing, transmission, and use of major data types.
- SOPs for use of the DMS.
- Data protection training for repository personnel (see *Section E. Training and Competency*).
- Verification and validation for data entry, data use, and data systems.

- Conformity to appropriate regulations and any data industry standards applied by the repository (see *Section C1.2. Legal Implications*).
- Data response planning including data backup (see *Section B2.3. Emergency and Disaster Preparedness and Response Planning*) and data disposal (see *Section K4.3.2. Data Disposal*).
- Software system(s) provision (including evaluation of the provider for expertise, implementation, support, ongoing maintenance, cybersecurity, and cost, where relevant (see *Section A4.3. Contracting Services and Consultants*).

***BEST PRACTICE:*** Repositories should have a Data Management Plan that identifies and describes the data which may be collected, used/generated, stored, managed, protected, transferred, and any data systems used. A DMP should also address data governance, risk assessment, security, sharing/transmission of data, and alignment with applicable regulations, standards, or guidelines.

***BEST PRACTICE:*** Stewards of the data should organize the data that is easily retrievable by personnel with the appropriate security access roles.

## I2.2. Data Management System

When planning a DMS at a repository, knowing or at least estimating its end-to-end use is a critical first step and should be re-evaluated periodically as part of quality management (see *Section D3.1. Quality Manual*). Use of principles such as FAIR (Findable, Accessible, Interoperable, and Reusable) and ALCOA+ (Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring, Available +) can assist as baselines for making decisions and guiding SOPs to ensure that the data collected will be fit for its intended purpose[1].

When deciding on DMS options, data types will be an integral consideration, as not all platforms support all data types. For example, a database that can handle massive files (*i.e.*, binary large objects, or BLOBs) may be needed for storing images unless the files are stored in a separate data source linked to the system. Future scalability or an expansion of the scope of work should be taken into account, both in regard to the systems and data.

DMS can range from the simplistic (*e.g.*, spreadsheets or paper-based documents) to large proprietary systems (*e.g.*, enterprise, cloud based). An initial step is to create a detailed checklist of requirements for a system, see ISBER Information System Evaluation Checklist[2]. Prospective end-users should be consulted in this process. Items in the checklist can be deemed as essential or desired. This provides a basis for reviewing system options. Cost, sustainability, expertise, and infrastructure are critical components to consider in selection. Open-source options are highly flexible but require skilled developers to build, maintain, and update the system. Off the shelf licensed systems generally require fewer skills to implement or modify the base system but can be expensive and may have limited flexibility. The repository should have SOPs relating to the DMS, including for the IMS (see *I3. Inventory Management System*). Such SOPs outline how the DMS is used, role-based permissions, and how the system is secured.

### I2.2.1. Categories of Data

There are several main categories of data that can be managed or linked at a repository. Some examples of these include:

- Participant and/or donor: Human, animal, environmental, ID, study species, study enrollment data, and location.
- Specimen: Geographical source location, type, site, identification, volume or mass, concentration, preanalytical variables, processing information, storage condition and location, and quality data such as images and cold chain provenance. See *Sections I3.2. Specimen Descriptors*, *I3.3. Data for Repositories Hosting Human Collections*, and *I3.4. Information for Biodiversity, Environmental, and Veterinary Specimens* for more examples.
- Research/analytical data: Resulting from assays of specimens and/or the data associated with the source (*i.e.*, clinical, phenotypic, omics, or image).
- Operational data: Management and oversight, quality management, reporting (training, risks, incidents), access for end-users, client information, facilities and equipment, and planning activities.
- Stakeholder data: A diverse category that includes external data, data from research results, public data repositories, networked or virtual platforms, and regulatory or certification/accreditation bodies.

Several other categories of data may be as critical to the operations and sustainability of repositories. An area of growing interest is information about the specimen collection as a whole, as it may contain emergent information on populations. Such information may assist the repository to meet inclusion and other goals or for sharing with stakeholders, including communities, end-users, and funding bodies.


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Operational data, such as that collected on equipment health, storage capacity, turnover of staff, training, growth of facility, user base, and utilization rates of collections, can help support the overall strategic planning and operational goals of the repository. Key performance indicators (KPIs) are used extensively in quality assurance (see *Section D3.8.4. Key Performance Indicators*) to track quality metrics and can be used to track important parameters generated from operational data, *e.g.*, specimens processed per month, reimbursement, and average processing time. It is useful to select KPIs that align with the repository strategic business and mission goals (see *Section A3.2.3. Components of a Business Plan*). Identification of these KPIs should be done at the planning stage but may change in later phases. The tracking and reporting should be automated if possible and the statistical and analytical methods formalized to ensure routine, consistent, and dependable data.

## I2.3. Data Security and Privacy

Although security and privacy are ubiquitous terms in today's society, it is important that these are not overlooked or oversimplified when planning a new DMS or new collections within an existing DMS. Given the nature and potential for misuse of the data contained in the repository, every effort should be taken to ensure that only those who are authorized can access the data, and that measures are in place to mitigate and manage any potential breach regardless of size or intent. Security and role-based access should be key components of a DMP. Security and privacy are paramount to protecting confidentiality of personal health information and research results (see *Section C2.1. Managing Research Risks for Participants*). Data security is the practice of safeguarding the digital information by preventing unauthorized access and modifications, malware installation, theft, corruption, misuse, destruction, and disclosure throughout its entire lifecycle. Data security measures should cover hardware, software, user devices, servers, computers, administrative and access controls, and organization's policies and procedures.

### I2.3.1. Data Security

Key mechanisms for data security include access control, access authentication, and data encryption.

- Access Control:

Administration of the user role is critical to data security (see *Section B1.4. Assessment, Control, and Monitoring of Risks*) and should be described in the DMP. Each user should have the minimum level of access required to undertake their tasks. In addition, the following is recommended:

- The administrator should define each user role, the associated access permission, and the potential impact on data. The user roles can be predefined for different categories based on the job description or scope.
- The repository should explicitly define which roles have access to confidential and sensitive information.
- A role-based access permission matrix can assist with managing roles and security. Each person should be assigned a role-appropriate access level. This should be reviewed periodically, or at minimum when roles change. In particular, access should be rescinded when an individual leaves the organization.
- Access Authentication:

Ransomware attacks are becoming more frequent and sophisticated and can inflict catastrophic damage on a repository, particularly for sensitive data. A repository should manage the risk of cyberattacks considering the potential impact on data and stakeholders and adherence to regulations, and apply access control measures appropriate to the risk (see *Section B. Risk and Disaster Management*). Possible control measures include:

- Protection against use of shared credentials and default passwords, and the unauthorized downloading of sensitive information.
- Validating and auditing authenticity of electronic signatures or other forms of identification/authorization (*e.g.*, thumbprint or other biometric scans). All e-signature events should be associated with the relevant date and time (see *Section D3.2.1. Creation of Documented Information* for information on time and date format).
- Storing of documents with hand-written signatures in a secure location, with representative signatures of all personnel with signing authorization securely stored for comparison against signed documents, to prevent forgery.
- Use of multi-factor authentication (MFA) or two-factor authentication (2FA) to facilitate extra layers of security between the data and anyone attempting to access the data. 2FA may use an additional text-message, app-based verification, or some other method in addition to a username and password to authenticate personnel accessing the data. Several methods of authentication exist that do not require internet access or costly equipment (such as challenge questions or additional codes). MFA and 2AF is a cybersecurity tool. Hackers may be able to get to the system but access to the data is further restricted.

- Data encryption:
  - » Encryption is a process that uses a code or encryption key to alter data in a way that makes it incomprehensible to unauthorized viewers. The code or key should be securely kept, separate from the data. Encryption can be performed on locally-housed data as well as on data that is being transferred and is of particular use to protect sensitive data. Examples of where encryption can and should be applied include databases, data backups, and data-in-transit. See *Section K4.2.2. Data Transfer* for additional information. Transfer of data should be performed only through approved, encrypted channels that are validated prior to deployment. Transporting or copying of sensitive data on private devices including USB drives and private email accounts should be avoided at all times. If data are to be transferred on external drives, the drive should be encrypted, not be the only source of the data, and should not include sensitive data.

Data security can be improved through the following measures:

- Regularly running a comprehensive antivirus program and firewall software, *e.g.*, nightly maintenance program capable of malware detection, quarantine, and removal.
- Physical security of location to control manual access.
- User role access control.
- User access authentication, *i.e.*, strong passwords and good password hygiene, multiple layers.
- Periodic maintenance and updating plan for devices used to store and access data (many updates contain security patches).
- Decommissioning of equipment and/or software that is no longer serviced or is beyond end of life with removal/destruction of stored data (see *Section H12.2. Repair or Replacement*).
- Encryption of sensitive and confidential data.

***BEST PRACTICE:*** To protect against unauthorized data access, repositories should employ multiple physical and electronic layer(s) of protection.

***BEST PRACTICE:*** To protect against unauthorized release of sensitive and/or confidential data, repositories should have strict physical and procedural controls for the use of personal storage and transfer devices and channels by personnel and other stakeholders.

### I2.3.2. Data Privacy

More countries and regions are taking a stand about how their citizens' data are handled *e.g.*, European Union's General Data Protection Regulation (EU-GDPR), the California Consumer Privacy Act (CCPA), and the South African Protection of Personal Information Act (POPIA). This is a key consideration when looking at where a database will be housed, from whom data will be collected, and with which countries or regions the data are intended to be shared. Everything from consent forms to how data can be used, generated, and distributed/disposed may be impacted by the region/country that will host the data or from where participants originate (see *Section C1.2. Legal Implications*). Privacy of data can be a concern with respect to protecting participants/donors/providers, resources, environmental ecosystems, and biodiversity (*e.g.*, protection of location coordinates of endangered wildlife populations). See related recommendations for confidentiality in *Section A4.2. Repository Personnel*.

The issue of confidentiality extends to end-users in receipt of confidential and/or sensitive data (see *Section K3.1. Contents of Transfer Agreements*). Such an agreement should prohibit the release of sensitive data, information, ideas, transaction details, and any other confidential data to third parties.

## I3. INVENTORY MANAGEMENT SYSTEM

Effective tracking systems should be in place to ensure that specimens can be tracked accurately from the site of collection through any transportation and processing, and through their entire lifecycle at the repository. Critical components of these systems include the use of specimen identifiers/labels, electronic data inventory systems for specimen tracking, consent form and/or permit tracking, and other features.

The inventory management system (IMS), sometimes referred to as a laboratory and/or biobank information management system (LIMS/BIMS), is a type of DMS that enables repositories to collect, store, organize, and share accurate data associated with specimens in multiple formats in an efficient and secure manner. An IMS should be capable of safeguarding the donor/participant privacy, confidentiality, and be set up to help ensure compliance with relevant regulations. It should additionally


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enable inventory and location management relevant to the storage units and the internal storage configuration (e.g., rack, box, row, column) and storage unit properties (see *Section J8. Specimen Inventory Management*) maintenance features, back-up capability, audit support, and support data integration and expansion, as required.

Selection of an IMS and the decision to build or buy depends on a number of factors that are unique to each repository's purpose and size. These include cost of ownership, fitness for purpose based on end-user requirements, ease of customization, time to implement, maintenance cost, and availability of ongoing support. Repositories may choose from a range of commercial or non-commercial off-the-shelf software programs, many of which can be configured or customized. Alternatively, the repository may choose to build a fully customized system. ISBER has developed a checklist to assist in selecting the best fit[2].

Procedures for validation and documentation of the system including backup routines should be developed as a written policy and included as part of the repository quality management. Software bug tracking, troubleshooting/help desk functions, and resolution procedures should also be documented and maintained (see *Section D3.2. Documentation Management and Control*).

***BEST PRACTICE:*** An inventory management system should enable reporting of all data elements to support audits of data and should have the interoperable capability to link specimens with associated data (*i.e.*, clinical, demographic, pre-analytical) through the use of identifier(s) unique within the system.

## I3.1. Specimen Location

Each freezer, refrigerator, room temperature storage cabinet, or other unit used for storing collections should have a unique identifier. A convention should be established for numbering shelves, racks, boxes, as well as each location within the box. The environment of the storage system should also be recorded, such as temperature and/or humidity, and these records should be maintained long-term. The system should also be able to capture data relevant to different types of containers used that do not follow the box/row/column configuration. Examples include containers such as straws, goblets, tissue arrays, and plates.

Each location combination (*e.g.*, building, room, freezer, rack, box, row, column, slot) should uniquely identify a storage location in the repository. Fixed compartments in liquid nitrogen tanks and upright freezers need to be uniquely identified, as well as any boxes placed therein. These components should have barcodes (1 or 2D) or an alternate type of identifier (*e.g.*, radio-frequency identification [RFID] tags) for location management purposes in the IMS. For example, specimen locations in boxes are linked to racks or compartments in the freezer. The IMS should identify different storage units within the same repository and should also record the container type (*e.g.*, vial, plate, slide, cassette, straw). The IMS should facilitate bulk upload of information. This could be through a spreadsheet or a plate read of bottom-barcoded vials. The IMS should enable reporting on available vacant storage space and provide capability to automatically assign and to reserve space for incoming specimens. The IMS should enable specimen location during audits (see *Section D3.7. Auditing for Performance Review*) and for tracking purposes (see *Section J8. Specimen Inventory Management*).

Changing the location of a specimen, individually or in its box/rack, should be tracked in the audit trail (see *I3.6. Audit Trail and Traceability*). The system should allow for mass movement of specimens where required, *e.g.*, an entire box or rack, and efficiently document the movement of large numbers of specimens, *e.g.*, when a freezer fails.

***BEST PRACTICE:*** The properties of the freezer or other storage units and its internal racks should be maintained in the IMS (*e.g.*, type, location, temperature) with the use of identifiers (*e.g.*, barcodes [1 or 2D], RFID tags on the components and/or freezers).

***BEST PRACTICE:*** To audit specimen location, a randomly generated specimen list should be physically checked on a subset of the stored specimens on a periodic basis to ensure that the correct specimens are in the location specified by the IMS (see *Section J8. Specimen Inventory Management*).

## I3.2. Specimen Descriptors

The IMS should determine the information to be tracked such as specimen type and identifier (see *Section J3.1. Identification and Labeling of Specimens*); vial or container type; specimen amount; date and time of collection; collection method, data, and time of receipt and/or processing; processing method; storage temperature; preservatives; thaw events. While the repository is ultimately responsible for identifying and defining the specimen descriptors that are relevant to the processes and activities, prospective end-users (where known) should be consulted for inclusion of any criteria relevant to fitness for purpose (see *Section D1. General Introduction to Quality Management*). Information should be recorded on the handling

of the specimen at each stage of the lifecycle including during entering of data into the system and the site at which each event occurred. Information should be included on the history of the specimen, including the tracking of shipments to and from external sites. Finally, any information about deviations from protocol or the specimen being compromised in any way should be recorded and available to the system (see *Section D3.8.1. Non-Conformities*).

The IMS should also be able to store or link to 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 (*e.g.*, consent, clinical, demographic, pre-analytical) for specimen selection, reporting, and other activities at the repository. Also, conditions listed in consent/authorization, transfer agreements (see *Section K3. Transfer Agreements*, or permits for the original collection of the specimens may require provision of information to the provider source or country.

The system should track significant events in the lifecycle such as specimen collection, warm and cold ischemia time during receipt, thaws, processing start and stop time, and outliers or deviations from protocol (see *Section J3.1.3. Tracking and Traceability*). The current state of the specimen including volume/quantity, specimen integrity, quantity remaining, movement of the specimen within and outside of the repository, and destruction are also important. Full query capability for all data stored should be provided.

Repositories may manage data created through the assay of the specimens or data associated with the source (*e.g.*, clinical, phenotypic, imaging, etc.). This data can be stored within the IMS or linked to an external system. Factors to be considered are size and complexity of the data, capacity of the IMS to store, and capability of linkage to external systems.

Descriptive information included in the IMS should avoid free text in data fields and preferably use predetermined pick-lists to standardize data and allow for accurate searching.

Although not a comprehensive list, the following basic specimen descriptors should be assigned and tracked (recommended descriptors and examples for specific collections from Humans, Biodiversity, Environmental, and Veterinary Specimens are additionally found in *I3.3* and *I3.4*, respectively).

- Specimen ID, study name, current label.
- Specimen information.
- Collection procedure.
- Type/category of specimen collected.
- Volume/amount.
- Processing information.
- Preservative/fixative methods.
- Storage conditions.
- Quality information.
- Parent-child relationships of specimens (aliquot or derivative) from the same source.

***BEST PRACTICE:*** The IMS should enable tracking of specimen and associated data (see *Section J. Specimen Collection, Processing, Receiving, and Retrieval*) with query capability throughout the specimen and data lifecycle.

## I3.3. Data for Repositories Hosting Human Collections

The information stored in the IMS will vary according to the purpose, nature, size, and intended uses for the collection. Since a repository may track specimens of many different studies and organizations, consideration should be given to the appropriate scope of information to be contained in the IMS locally and what should be stored in an external database and linked to the inventory.

The repository should ensure that any other systems are interoperable with the repository IMS. If the IMS includes a comprehensive clinical database, additional requirements may pertain (*e.g.*, clinical trials, recording adverse events, incidental findings). The repository should ascertain what data needs to be accessible relevant to the requirements. It is suggested to refer to Good Clinical Practice (GCP), and local and national legal and ethical requirements for a more comprehensive list of requirements to ensure compliance.

Types of Information that should be collected include:

- Identification, *e.g.*, study name, participant/donor ID, specimen ID, label.
- Demographic, *e.g.*, name, date of birth, sex, gender, race, ethnicity, address, email address.
- Clinical, *e.g.*, medical history, diagnosis (name and/or classification such as ICD10 codes), symptoms, treatment, medication, tests (*e.g.*, imaging, cognitive, hormone levels) and results.
- Lifestyle and environment, *e.g.*, smoking, diet exercise, occupation, exposures, climate.



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- Specimen collection/acquisition, *e.g.*, type of procedure (*e.g.*, surgery, biopsy, blood draw), procedure location, procedure details (*e.g.*, surgical pathology number).
- Specimen, *e.g.*, tissue (*e.g.*, cardiac tissue), biofluid (*e.g.*, blood, urine), tissue type (*e.g.*, normal, sarcoma), pathologic stage.
- Processing: extraction method, lyophilization method, hemolysis, fixation.
- Quality control, *e.g.*, concentration, integrity (*e.g.*, DIN, RIN for nucleic acids), hemolysis, viability, species confirmation.
- Other characterization, *e.g.*, percentage tumor, inflammation status, percentage necrosis, sequencing data, strain phenotypic characteristics.

An IMS can also be designed so that digitally scanned documents and images are included or linked to the system through a specimen ID, such as pathology reports, slide images of tissues collected, clinical lab reports, donor consent forms, and transfer agreements (see *Section K3. Transfer Agreements*). Since sensitive and personal data are often a part of such documents, measures should be taken to protect security and privacy (*e.g.*, redacting information and role-based security) (see *I2.3. Data Security and Privacy*) when scanning.

#### I3.3.1. Anonymized Data

For collections to be anonymized within the IMS, the repository may first define which data fields are deemed personal/sensitive data, identify corresponding personal data fields/tabs in the IMS form(s), and block these from being completed during data entry. The repository additionally needs to consider how data can be represented to remove sensitivity (*e.g.*, using *age* rather than *date of birth*, etc.). However, anonymization may be more difficult when it comes to rare and very rare disease collections, as different combinations of data elements might suffice to identify the participant or a familial association. A repository should consider that such a collection might never be truly anonymized. Therefore, data security measures should be in place when sharing such data, *e.g.*, determining that end-user justification for each data element is in accordance with ethical and legal approvals in place (see *Section K2.2. Review of Access and Use Requests*). It may additionally be possible to test for identifiability using different combinations of data elements (particularly for a long-standing collection or where federated biobanks exist) and then only distribute specimens with a minimal set of non-personalized data elements.

### I3.4. Information for Biodiversity, Environmental, and Veterinary Specimens

Many types of information listed in I3.3. are also applicable for biodiversity, environmental, and veterinary specimens. 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, and microorganism repositories or environmental specimen banks (ESBs)[3]. 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 facilitate academic discussion, research and clinical auditing. Natural history collections use globally unique specimen identifiers for their specimens, usually accomplished through the so-called 'Darwin core triplet' (institution:collection:specimen ID), see *I3.8 Data Standards*.

Types of information that can be further considered for collection include:

- Species: Genus/species name.
- Common name.
- Specimen source Identification number(s), *e.g.*, national herd number/animal number.
- Research study/collection name.
- Permitting agency(s), if applicable.
- Permit number(s), if applicable.
- Site ID, *i.e.*, the location where the specimen was collected.
- Global positioning system (GPS) coordinates, *e.g.*, latitude and longitude; details of sampling location to the nearest tenth of a minute, where practicable.
- Collection time and time of death, where relevant: Recorded as day, month, year.
- Storage and transfer conditions, *e.g.*, critical temperature ranges.
- Sex: Male /female/other.
- Length, measured in meters.
- Weight, measured in kilograms.
- Description of condition, including relevant codes of decomposition where deceased.
- Specimens collected: Indicate specimens collected and for what purpose; histology, virology, genetics, and contaminants[4,5].

- Health certificate, if applicable.
- Biosafety information (see *Section F4.1.1. Biosafety*).

### I3.5. Virtual Platforms

Virtual platforms are digital searchable databases of specimens and their associated information which are generally physically independent of the storage of the specimens. The benefits of such platforms include informing potential end-users of existing collections, and increased utilization of specimens and/or data collections. Often facilitated through a singular common interface or linked systems, general information on specimen collections (*e.g.*, specimen types, data variables, quality, etc.) from repositories can be made available to prospective end-users. Furthermore, these types of interfaces can often provide the ability to request access to the physical specimens and/or data for distribution. Several models of virtual platforms based on functionality exist including federated, catalog, and negotiator models. An overview of some of these is provided along with considerations for interoperability, harmonization, and systemization of data. Virtual platforms present unique opportunities, benefits, and risks[6]. Two types are presented below: federated platforms and digital catalogs/directories.

- Federated platforms: These include data from a network of multiple repositories or collection sites which may be geographically separate[7-9]. The sites may be part of the same research study, with common protocols and SOPs, or linked through a shared disease or population focus. Each repository or site functions as the specimen and data custodian for the local collection. Specimen-related data from each site is additionally managed or duplicated in a central database. Approved prospective end-users can request specimens and/or data through this federated database. Federated network participation may require that a portion of each site's collection be made preferentially available to other network participants. Participation by repositories within a federated platform may require the use of standardized terms and data elements when specimens and/or data are added to the central database in order to facilitate searches across the collections.
- Digital catalogs/directories: Digital catalogs are often an effective way for repositories to better enable access and improve specimens and data use rate[10]. A repository may wish to create a catalog or seek representation of their collections within existing digital catalogs as a way to promote their collections. A digital catalog or directory functions as a type of virtual platform. Catalogs provide access to descriptions of collections for external stakeholders. The ability to request specimens and/or data may be an additional feature of a digital catalog. The primary goal is to maximize efficiency of finding and distributing specimens and/or data that are already collected and available in repositories. Catalogs can provide researchers a valuable resource to search locally and distantly for fit for purpose (FFP) specimen types with associated phenotypical, clinical, and other data categories, relevant to research requirements. As is the case for federated platforms, digital catalogs may be supported by a common interface/portal that allows potential end-users to search for available specimens and/or data from a single organization or multiple organizations[11-13]. Often, these collections were not collected under a common protocol. Some IMSs provide a catalog-generating feature. The catalog may list the available specimen types, data categories, as well as the collection/repository from which they are derived.

A virtual platform may additionally provide functionalities for:

- Cost recovery.
- Additional end-user requests, such as prospective collection of specimens and/or data tailored to meet specific research purposes[14-16]. This can be useful when specimens and/or data necessary to support a particular research purpose are not available or accessible. The request is generally reviewed at the repository to determine feasibility of fulfilling the request.
- Expediting or negotiating between the various repositories and end-user parties.

There are many general considerations associated with the setup and the operations or participation with any type of virtual platform. Relevant considerations include:

- Any adverse impact on the existing repository policies and governance or agreements (*e.g.*, original or prior consent, transfer agreements, permits) relating to the intended transfer, storage, and use of the specimens and/or data outside of the region of the source repository.
- Any additional ethical, legal, and social implications (ELSI) beyond the scope of the original collection and source repository.
- Security, access controls, data integrity, interoperability, and privacy controls.
- Additional resources may be required to fulfill any platform requirements prior to participation (*e.g.*, for harmonization of terminology, and classifications of specimens and associated data).


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- Access for stakeholders of differing abilities (*e.g.*, sight, hearing) may be regulated by the parent organization or countries of the specimens (*i.e.*, when setting up a catalog).
- That the virtual platform provides a FAIR-principle solution toward increased utilization of existing stored specimens and data, (see *Section C1.4. Fairness and Equity in Repository Planning and Operations*).

## I3.6. Audit Trail and Traceability

An audit trail that tracks and traces data changes is an essential tool for ensuring data integrity. An effective audit trail covers all levels of repository data including specimen data, operations, and system data. The IMS automatically records data entry and changes to data including but not limited to: original data, changed data, who made the changes, how the change was made, date and time of the change, and if possible, why the changes were made. Previous or original data should not be obscured by edits or changes[17]. Traceability is key to specimens and or data provenance and it should be possible to determine the source data point and quickly trace its origins back to its raw source, if necessary.

If sensitive or personal data is stored in the system, an audit trail may be required by regulatory or other authorities. In such cases, the repository should ensure that every instance of accessing or reporting the data is documented in the audit trail with the date, time, and name of the person accessing or reporting the data[18, 19]. A repository should include practices to ensure that if a donor/participant requests a list of all persons viewing their sensitive data, reports can be readily provided (see *Section D3.2.3. Retrieval and Availability of Documented Information*). This audit trail should be available to system administrators for read-only access, be searchable and able to be reported electronically, and be clearly defined in an SOP[19]. Such documentation should be retained for a period at least as long as that required for the electronic records and be available for audit (for further information on auditing, see *Section D3.7. Auditing for Performance Review*).

***BEST PRACTICE:*** IMSs should have full audit trail capabilities to provide information on any changes to the system, date and time of the change, who made the change, and why it was made. Data audit reporting should be available to those in authority at the repository or the organization.

***BEST PRACTICE:*** A scheduled, planned, and well-defined audit of the database should be performed to ensure accuracy of data, and measures taken to correct incorrect data or complete missing data.

## I3.7. Interoperability, Portability, and Reconciliation

Integration and interoperability of data are critical within modern informatics systems. Systems should be able to integrate with other related applications, such as electronic medical records, clinical registries, pathology systems, and storage unit temperature monitoring, as required. This also allows for individual repositories to share data associated with specimens across networks and systems safely and efficiently (see *I3.5. Virtual Platforms* and *I3.9. Cloud Systems*).

Interoperability is the ability of two systems to talk to one another (*i.e.*, to exchange messages and information in a way that both can understand), interacting on a regular basis. This interoperability may be between two IMS platforms or between separate databases. This interoperability can also include communication between a data system and connected assay equipment or devices that may be the sources of data that is being collected in the data system. These connected data sources may be within the repository or external to it.

### I3.7.1. Data Portability and Interoperability

There are many scenarios in which a repository might transfer or receive specimen-associated data to other groups, including distribution from approval for access, loans, or transfer of collections and migrating to a new IMS; catastrophic events; and relocation to a new custodian (see *Sections K4. Transfer and Disposal* and *G10. Relocation of a Repository*). Data portability is the ability to move data (files, documents, database tables, etc.) from one system to another, and have that data be easily usable. Interoperability for integration of data has many benefits including, but not limited to, the following[20]:

- Reduced re-entry of data. When data is manually re-entered from one system to another, there is a risk of error introduction. Re-entering data can be costly in personnel time to reconcile new entries.
- Data errors found and corrected in the primary system need not be replicated to other systems.

Data should be electronically convertible into formats that can easily be shared among collaborating organizations, where possible and appropriate. Planning for this conversion should be done in preparation of installing the IMS at the repository. The IMS should enforce all data integrity, security, and audit trail requirements for external access. A growing practice, termed legacy data migration, is to incorporate external data libraries (and/or specimens) into current repositories. This may include libraries on loan (*e.g.*, museum collections) or the integration of legacy

collections. It is paramount that the IDs, associated data, be integrated fully into the current IMS (for more information see *Section J3.1. Identification and Labelling of Specimens* and *I3.8 Data Standards*). To achieve interoperability, the IMS should include the following[21]:

- Functionality to enable integration with other systems, *e.g.*, public documented application programming interface (API).
- Use of relevant standardized data vocabularies (*e.g.*, SNOMED, ICD-9-CM, ICD10, ICD-O).
- A framework that allows connection to other systems and to communicate with external APIs on an event-driven or periodic basis.
- Operation in accordance with the repository and institutional/organizational data sharing policy.

### I3.7.2. Data Reconciliation

Data Reconciliation is the process of data validation through identification of data errors and a set of protocols and actions for rectifying them (see *Section D3.4.2. Data Quality Assurance*). Data reconciliation may be performed at any point, but is critical during data migration and transport, audits, and new data system platform integration[22,23]. Verification of data integrity during data migration or transfer of data between systems (*e.g.*, between a clinical database and the repository IMS) is imperative. In this process, target data (data that have been transferred or migrated) is compared with source data to ensure that the migration is correctly transferring the appropriate data.

Reconciliation may be as simple as running basic descriptive statistics (*e.g.*, mean, median, minimal, and maximal values) on the new data that have been transferred, or it may be more complex database comparisons, *e.g.*, queries looking at specific subsets of the data for cases when an entire database is transferred. The reconciliation process should be noted in the DMP (see *I2.1. Data Management Plan*) and other supporting documentation to ensure that the appropriate checks are being completed at an agreed-upon schedule.

Errors in data elements of values to search for during a reconciliation include the following[24]:

- Missing records.
- Missing values.
- Incorrect values.
- Duplicated records.
- Badly formatted values.
- Broken relationships across tables or systems.
- Correct coded values and calculations.

A list of agreed-upon checks should be developed. This list should not be so long that it becomes too time-consuming to run through, or too short that key variables/relationships are overlooked. Once the list is developed, a workflow for correction needs to be created and signed off on by participating sites. This may include quarantining the records in question, generating a report for the sites to review, or other methods (or combination thereof) to ensure the data is corrected (remediation) in a timely manner.

Data Reconciliation can be a time-consuming task, especially in the initial stages of a repository, but the long-term consequences of not doing this on a regular basis could prove to be significant and result in data that are unusable.

***BEST PRACTICE:*** Data reconciliation should be considered and designed from the very beginning with a comprehensive list of checks to be developed along with schedules and workflows for correction/handling of discrepancies.

***BEST PRACTICE:*** Data portability and interoperability considerations include ensuring any required mapping data is stored in the IMS.

### I3.7.3. Data Attributes for Quality and Interoperability

For optimal interoperability, key data attributes of the specimens should be shared, whether it is the transferring of data across virtual platforms (see *I3.5. Virtual Platforms*) or within manifests of specimens physically shipped to other repositories (see *Section L4.1. Shipping Manifest*). Having extensive and robust data associated with specimens ensures usability as well as maintaining quality standards (see *Section D3.4.2. Data Quality Assurance*). Robust annotation of specimen collections can additionally support biobank management and operations, emergency management planning, and stakeholder engagement. Standard key data elements include variables such as: specimen type, study type, fixation/stabilization methods, and mass or volume, including units. However, to support full utility of transferred collections, seeking additional specimen annotation, as available, for collections or human trial studies is preferable. The following items may be needed to document human specimens:


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- Participant/donor ID (linked to specimen ID).
- Date collected/drawn.
- Visit number (as applicable).
- Collection center.
- Type of collection.
- Processing details (link to SOP).
- Vial/container type.
- Vial warnings (thaw number, other quality information applicable).
- Subject ID linkage to clinical data (data may not be held at in the IMS).
- Subject ID linkage to phenotypic data (data may not be held at in the IMS).
- Linkage to collection replicates/aliquots existing at different sites (multi-site network).

Other important information not directly associated with the specimens that may be needed for human biological materials that are shared from the original collection site may include:

- Consent type (*e.g.*, broad or specific/restricted; see *Section C. Ethical Legal and Social Implications*) with a secure link to documentation.
- Linkage to governance plan of specimen collection (documentation may not be held at repository).
- Allowances or restrictions on access for sharing (see *Section K2.1. Access, Distribution, and Use*) expressed within transfer agreements (see *Section K3. Transfer Agreements*), including any anonymization requirements, as applicable that might dictate a need for relabeling/de-identification.

## I3.8. Data Standards

The IMS should use standard data elements and avoid usage of free text fields, as much as possible[11, 25, 26]. Standard data elements enable better database processing such as searching and sorting, which is an integral part of DMS. Data entry validation strategies include drop-down lists or pick lists for associated annotation and pre-analytical variables being tracked (*i.e.*, specimen type, cold ischemia time, fixative, body site of collection, study name, freezer IDs). Such use of categorical data options can benefit enhanced data quality checks, data mining and analysis, and faster data entry that is less error-prone. Using "other" text boxes (an option which facilitates the user to manually enter a new category other than that listed) allows for real-time opportunities to update the categories in the event that new options are to be added.

The IMS should facilitate recording why data is missing, *e.g.*, not available or not applicable. IMS should also allow data to be translated into established data standards (*e.g.*, from protocol-specific disease categories into MedDRA) even if non-standard data elements are used.

Documentation of a system should include an accessible data dictionary or codebook, which includes at minimum the names and definitions of data elements and also may include data type, ranges, data format, type of data, and rules for validation of data. A data dictionary facilitates standardization by documenting common data elements. The use of standard data elements and a shared data dictionary provides the precise vocabulary needed for discussing specific data elements in a shared system such as a specimen and data catalog.

Several data standards for repository operations exist for application in different scenarios. Although not all standards will be applicable to each repository model, use of specific standards can help assure meeting FFP data goals (see *I1. General Introduction to Information Management*). Standards include:

- BRISQ (Biospecimen Reporting for Improved Study Quality) is a standard to better understand, interpret, compare, and reproduce experimental results involving human specimens. The data elements are about participants, specimens, processing, and storage and are recommended for reporting for publication or for regulatory purposes[27].
- SPREC (Standard PREanalytical Code) is a short-hand code of seven pre-analytical variables related to specimen collection, processing, and storage. The SPREC is assigned to a specimen and any derivatives (see parent-child specimens, *I3.2. Specimen Descriptors*) and stored in the IMS. Specimens of the same type that have undergone identical collection and handling processes and storage conditions have identical SPRECs[28].
- MIABIS (Minimum Information About Biobank data Sharing) standardizes data elements used to describe repositories, research on specimens and associated data, with the aim to support interoperability between repositories[29].
- OBIB, the Ontology for Biobanking, is an ontology for repository data management and may be used for annotation of biobank data, and since an ontology provides information in both human readable and computer interpretable form, it allows for automatic knowledge generation and provides artificial intelligence (AI) capabilities. OBIB covers a broad spectrum of activities including specimen management and curation, and operational aspects. It also entails the basics of demographic and clinical data that typically accompany specimens[30].

- Informed Consent Ontology (ICO) represents the domain of informed consent, including: consent forms, policies governing informed consent, individuals working with patients and biospecimens accompanied by consent, and the process of informed consent itself. ICO aims to support informed consent data integration and reasoning in the clinical research space[31].
- GGBN, the Global Genome Biodiversity Network Data Standard, was developed in order to facilitate exchange of information on genomic specimens and their derived data. The (GGBN) Data Standard is intended to provide a platform based on a documented agreement to promote the efficient sharing and usage of genomic specimens and data in a consistent way[32].
- Darwin Core (DwC)[33] offers a stable, straightforward, and flexible framework for compiling biodiversity data from varied and variable sources. Originally developed by the Biodiversity Information Standards (TDWG) community, DwC is an evolving community-developed biodiversity data standard.
- LPSN, the List of Prokaryotic names with Standing in Nomenclature is a longstanding key resource for microbial taxonomy integrated recently with another bacterial nomenclature database Prokaryotic Nomenclature Up-to-date (PNU) by the Leibniz Institute DSMZ-German Collection of Microorganisms and Cell Cultures GmbH[34].
- ISO/IEC 27001 and related standards[35] — Information security management, including ISO 27701:2019, Security techniques — Extension to ISO/IEC 27001 and ISO/IEC 27002 for privacy information management — Requirements and guidelines.
- ISO 8000-1:2022 Data quality — Part 1: Overview[36].
- Access to Biological Collections Data (ABCD) Schema [37] - is an evolving standard for accessing, sharing and exchanging data related to primary diversity specimens and observational data.

## I3.9. Cloud Systems

Cloud systems deliver a wide array of services through the internet that can range from data storage (*e.g.*, data warehouses, data lakes) to complete software solutions (*e.g.*, IMS, analysis tools).

Cloud services providers (CSPs) are an entity separate from the repository 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 repository.

Cloud systems[38] offer many benefits to repositories. They can facilitate collaboration between different repositories or other entities, provide a high level of security by protecting data during transfer and offer rapid scalability to accommodate changes in operations. The data generated by repositories remains on the cloud system with only the tools and personnel that are authorized can have access. This functionality enables maintaining data privacy. Furthermore, such systems can play a key role in the disaster management plans of repositories given the availability of automatic data backups and mirror servers if a data center is hit by a natural calamity or a disaster such as fire or theft.

A repository that engages a CSP should evaluate the cloud system platform and conduct risk assessment based on a risk management policy (see *Section B. Risk and Disaster Management*). The system should ensure compliance with regulations/frameworks concerning ethical and legal issues[39]. The repository should enter into an appropriate contract or agreement and a service level agreement (SLA) with the chosen CSP.

Repositories seeking information about types of cloud computing services, cloud data management[40] 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 Information technology — Cloud Data Management Interface [CDMI])[41].

***BEST PRACTICE:*** Repositories should ensure that any cloud service utilized maintains the privacy and security of sensitive information as well be compliant with all pertinent legal and ethical regulations and/or guidelines.

## I3.10. Reporting from Inventory Management System

Reporting is an essential functionality of the IMS to support the repository workflow, and includes compliance frameworks such as applicable regulations, quality management processes, *e.g.*, auditing (see *Section D3.7.3. What to expect from an Audit Report*), and operational goals.

Reports may be issued as hard copy, electronically, or by electronic transfer to another system. Information to be provided within the report should include repository name, contact details, date of issue, a unique report identifier number, authorizing signature, and a statement that the report should not be reproduced except in full nor should it be shared without approval. Reports should be generated and maintained per document control standards (see *Section D3.2. Documentation Management and Control*). The data content of a report can be derived using a query functionality.



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The system should allow for the ability to run searches on the data to identify and select the specific data record. The system should have a graphic user interface (GUI) for querying data, displaying content, and generating reports. Data fields available on the interface can be controlled through role-based access rules. The exact nature of this interface can vary from full "what you see is what you get" (WYSIWYG) to simple field selection for tabular reports. The ability to search for specific data (run queries) can be accomplished by utilizing several approaches, including simple data query forms, Query By Example screens, customized query builders, and text areas for native query specification.

To ensure consistency, the IMS should have the ability to save report specifications (fields, metrics, etc.) for future execution and have the ability to modify these saved specifications as well as share the report specifications with other users.

The IMS may need to have the ability to generate reports in multiple formats (*e.g.*, in ASCII, XML, CSV, or XLS), for interoperability with analysis programs, readability, or presentation preference. The ability to view and generate selected predefined types of queries and reports may be linked with specific user levels. Sensitive personal data fields may be assigned as identifiable so that only designated users can be allowed to generate reports using these fields.

Additionally, the repository should maintain SOPs about the generation, use, and destruction of reports that contain sensitive personal data to ensure that donor/participant confidentiality is maintained[42]. Every instance of accessing or reporting the data should be captured in the audit trail (see *I3.6. Audit Trail and Traceability*).

***BEST PRACTICE:*** The IMS should save report specifications for future use to ensure consistency. Access to reports should be restricted to users with required permissions and sensitive information should be highly restricted.

## I3.11. Validation of Inventory Management System

Any new software or upgrade to existing software should be validated and assessed with dummy entries and retested before implementation. Validation (sometimes referred to as user acceptance testing) is an essential process to ensure that the system works as designed and intended.

Whether the IMS is a commercial off-the-shelf software or a customized 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.
- Operational system checks to enforce permitted sequencing of steps and events, as appropriate.
- Authority checks to ensure that only authorized individuals can access and 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.
- 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 are trained and deemed competent to perform the assigned tasks.
- The establishment of, and adherence to, policies that hold personnel accountable and responsible for actions initiated under their electronic signatures to avoid falsification of records and signatures.
- Appropriate controls of systems documentation including:
    - For 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 implementation validation, ongoing validation should be performed when the system is updated in a maintenance release or new features are added. The ongoing validation plan and process should be documented (see *Section D3.6. Validation, Verification, and Qualification*). 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.

One of the key components of testing and validating a system is the concept of reproducibility[43] or the ability to get the same results when the same steps are followed, the cornerstone of producing fit-for-purpose data. This means that when testing a system, feature, report, or even a workflow or process, one test "run-through" is not sufficient. Testing scripts should be written with explicit step-by-step instructions for the tester to follow, and the results should be identical every time.

After IMS testing is complete and all known bugs/process issues, etc., have been identified and resolved, the data generated from the testing should be extracted and provided for preliminary statistical or analytical review. This downstream

review of data is critical to determine if the system is capable of meeting the needs of the repository. Any reporting or other planned uses for the data should also be tested using this dummy data to ensure reporting requirements are met.

The final piece in testing a system is the backup and recovery model: how the system handles data during a power outage or if the connection to a server drops. Running through potential disaster scenarios help to provide assurances to stakeholders that a strategy is in place to keep data and specimens safe and secure (see *Section B2.3.3. Procedural and Operational Preparedness* and *I3.14. Data and Systems Backup and Disaster Recovery*). Tests can be performed with and without prior notification to determine how personnel react in a real situation.

The backup files should also be tested to ensure that the data program environment can be identically replicated in an entirely new one. Areas that need to be verified include but not limited to:

- Logs and any auditing information transferred.
- Hyperlinks and other links to intra- and extra-system data working as expected.
- User roles and levels of access properly transfer.
- Uploaded/attached files transferred over.

***BEST PRACTICE:*** The IMS should have comprehensive validation and verification procedures in place to ensure accuracy and intended performance. All validation and verification performed should be documented to ensure traceability and ongoing accuracy of the system.

***BEST PRACTICE:*** Part of a rigorous validation plan of an IMS should include testing the ability to reproduce consistent and correct actions when a standard set of data is entered. The system should be challenged on a routine basis to assure reproducibility.

## I3.12. Data Entry

To best support data quality (see *Section D3.4.2. Data Quality Assurance*), efforts should be made to ensure data are correctly inputted from the start to prevent reconciliation errors at a later point (see *I3.7.2. Data Reconciliation*). With data that are imported or transmitted to the repository, using data standards (see *I3.8. Data Standards*) and following interoperability guidelines (see *I3.7.1. Data Portability and Interoperability*) is key. Data entry is usually carried out by technicians or data entry operators/support personnel in the repository. Training and competence are critical for reducing input errors (see *Section E. Training and Competency*). Training should include data accuracy, security, privacy and confidentiality, data management systems, and amended data entry procedures.

## I3.13. Data Security for Inventory Management Systems

Data integrity as well as access control have to be considered. Data 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 to be kept secure to minimize threats to endangered species. As mentioned above, Cloud-based repositories need to have a clear understanding of the host country's regulatory requirements around data protection/storage as this may impact the backup plan/disaster recovery process.

Access to the IMS should be tightly controlled. Data security of IMSs should comply with general guidelines suggested with all information systems as described in *Section I2.3. Data Security and Privacy*. Security roles with defined privilege levels should be assigned to individual users of the system. Some individuals may be able to view specimen availability (*i.e.*, their custodial collections or full inventory), whereas others can enter or modify specimen records or descriptions and make requests to have specimens shipped from the repository. Depending on the size of the repository, the IMS may have a web-based view with fewer options for users to perform vs. the back-end client used by the hands-on repository management. All sensitive records should be secured within the IMS through role-based access controls and/or encryption. All remote communication should be able to be conducted on an encrypted socket. An approval process for providing access as well as an audit trail of users should be maintained. A review of users and their assigned roles should be carried out on a regular basis, *e.g.*, annually. This review process should be documented (see *Section D3.2. Documentation Management and Control*).

A repository should develop a system for archiving records that are not currently needed for regular activities but need to be retained for defined periods of time (see *Section D3.2.2. Storage and Retention of Documented Information*). This



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system should allow all archived records to be accessible for audits and inspection as defined in *Section D3.7. Auditing for Performance Review*.

***BEST PRACTICE:*** Repositories should use a computerized IMS that includes a role-based approach to security in which the system, application, transmission, and network are secured against unauthorized access and modifications. The IMS should be safeguarded from other systems that might pose a security risk.

***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:*** The system for data security should provide a mechanism for enabling and disabling IMS access, as well as restricting access to a particular time window/logging off users after a specified period of inactivity.

***BEST PRACTICE:*** Passwords should conform to the minimum institutional standards.

***BEST PRACTICE:*** Any physical documentation held onsite that contains sensitive information (*e.g.*, confidential donor/end-user information) should be locked in secure fire and waterproof 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 a procedure.

## I3.14. Data and Systems Backup and Disaster Recovery

Temporary or long-term data system outage or data loss can occur for various reasons including natural disaster, security threat, technical issue, etc. Planning for disaster recovery is presented in *Section B2.3. Emergency and Disaster Preparedness and Response Planning*. Emergency response tests should be performed periodically, evaluating the completion and accuracy of the plan as well as practicing roles and responsibilities. A contingency plan should be in place in case of such an event to minimize disruption to workflow. In some situations, it may be possible to reschedule activities but in time-sensitive scenarios this may not be possible. Where required, data activities deemed critical should be enabled offline and may include:

- Paper copies of participant/donor consent forms.
- Established procedures for:
  - Manual assignment of specimen IDs, *e.g.*, by setting aside a list of unique IDs for such use and/or have a list of all repository IDs in a separate software system or on paper to ensure no duplication and to ensure continuation of sequential IDs, where relevant.
  - Scanning of specimen IDs, barcodes, RFID, etc., to temporary spreadsheets including uploading to IMS when possible.
- Paper copies of required data forms for essential data collection.
- Paper copies of procedures.
- Scheduling activities: If the system is relied on for scheduling activities, regularly save a back-up of the schedule (*e.g.*, weekly, monthly) in another system or on paper.

Following system recovery, data entry of data accurately, consistently, and in a dependable manner should be enabled.

### I3.14.1. Data Backup

Electronic records should be routinely backed up (see *Section D3.2. Documentation Management and Control*). The database and server(s) should be backed up separately on a regular basis, depending on the repository policies and frequency of data modification. Backups should also be made when changes are made to the system, including applying patches or upgrading system-wide functionality. Backups of both data and systems should be made prior to changes being made (pre- or post-production) to allow for easier roll back if the implemented changes do not work as expected. Having a replicated DMS in a separate location may be a consideration for restoration with minimal downtime/loss of data in the event of catastrophic loss at the primary location.

A data backup plan (detailed in the DMP) to preserve the integrity of repository data should include steps to limit the extent of the destructive event, and detail procedures for:

- Periodic backing up and storing of information using an established backup schedule. Creation of a backup schedule should account for data backup and system backup. The more frequently the data are changed, added, or updated, the more frequent the backups that should be made. To create a data backup schedule, the repository should determine its tolerance for data loss.

- Secure storage of backup data, *e.g.*, off-site. The backups should be stored in a secure location, separate from where the system is housed, and should be accessible by personnel responsible for the repository information technology infrastructure.
- Recoverability of data by restoring information from backed-up media. System and database backups should be tested on a regular basis to ensure the data and server environment can be accurately recovered.

***BEST PRACTICE:*** Repository databases should be backed up frequently (daily, weekly) based on organizational protocols or frequency of database modifications.

***BEST PRACTICE:*** A contingency plan should be in place to minimize disruption to workflow and in the event the IMS is unavailable. The plan should detail how data will later be entered into the IMS. The plan should be tested and re-evaluated on a regular basis.

## I3.15. Data Associated with Shipments

Movement of specimens and data into and out of a repository is highly regulated and creates the need for the repository to document all packaging and shipping processes associated with the specimens and data, from the shipping logistics, to the events during shipment (temperature excursions, delays, and any damage), to receiving of shipment. The documentation associated with these processes (manifests, waybills, and shipment verification report forms, etc.) are important tools to track key data elements that should be stored in a retrievable format at the repository (often in the IMS). These data elements can be used in repository management and operations, and in access and use of collections. The processes and important data elements associated with shipping are described in see *Section L4. Documenting and Tracking Shipments*.

## I3.16. Data in Automation

Automation is the use of technology which replaces or enhances human actions that can be used in a variety of ways to optimize repository workflow. Automated devices and actions range from simple (*e.g.*, temperature-monitoring sensors and handheld barcode scanners) to complex robotic equipment which handle multiple or complex functions, *e.g.*, specimen storage and retrieval (see *Section H4. Automated Storage Systems*) and liquid handling (see *Section H11. Automated Liquid-Handling Robotics*).

Automated systems require data processing/programming and hardware systems and can impact fitness for the purpose of specimens and data generated by a repository. Understanding and managing the operational data, specifically with complex equipment, may create a need for an informatics solution within the DMP (*e.g.*, IMS that integrates robotic handling of specimen containers). Data concerns to address within complex automation include:

- Data backup plan (including manual backup plan with manual data entry; see *I2.1 Data Management Plan*).
- Site acceptance testing to ensure proper setup and functioning.
- Interoperability validation between integrating systems.
- Maintenance, service, and warranty agreements.
- Ability to generate audit trails.

***BEST PRACTICE:*** Automated actions within the workflow should be documented end-to-end and validated against a manual process, prior to the automated process being implemented. Automation needs to be tested on a regular basis to ensure accuracy and consistency (see *Section D3.6. Validation, Verification, and Quantification*).

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# SECTION J: SPECIMEN COLLECTION, PROCESSING, RECEIVING, AND RETRIEVAL

## J1. GENERAL INTRODUCTION TO SPECIMEN COLLECTION, PROCESSING, RECEIVING, AND RETRIEVAL

A specimen life cycle includes all of the activities associated with the collection or acquisition, storage, distribution, and disposal of a specimen and its associated data. It may include externally provided processes under the control or management of a repository. It is acknowledged that activities after distribution to end-users external to the repository are generally not under the control of the repository. This section will focus on the processes and activities associated with the specimens themselves. See *Section I. Information Management* for recommendations and best practices for the data associated with specimens.

Specimen collection and retrieval practices have many elements in common, while specimen processing varies 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 (see *Section D1. General Introduction to Quality Management*), and methods should be used to ensure that all specimens collected are fit for purpose[1] (see *Section D3.6. Validation, Verification, and Qualification*).

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 additional criteria required for the preservation of specimen viability, functionality, structural integrity, and stability. In addition to specimen type, other considerations prior to initiating a collection include regulatory, safety, and legal/ethical issues (see *Sections C. Ethical, Legal and Social Implications* and *F. Health and Safety*).

Specific personnel responsibilities, training, risk management, and skills may be required for specimen collection (see *Sections A4.2. Repository Personnel* and *E. Training and Competency*). 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 a different location). Standard protocols for specimen collection and handling should be established and followed. Protocols for stabilization and/or preservation of specimens during transit may be necessary.

Due to the potential impact of preanalytic processes on specimen quality, it is important to apply strategies that maintain the stability and functionality of specimens and macromolecules of interest (see *Section D3.6.3. Preanalytical Variation*). 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 and repository purpose (see *Section A1.1. Types of Repositories*), many different specimens may be collected, processed, and/or stored from the same participant/donor source 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). Having redundancy of specimen types can maximize the opportunity for future usage. However, limitations imposed by processing time requirements and the repository's storage capacity should 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 specimen integrity or freeze/thaw events.

***BEST PRACTICE:*** The time, temperature, and the person handling the specimen should be documented every time a specimen is manipulated.

## J2. 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 help to identify problems or critical points and instigate preventative actions 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.



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## J3. 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. Specimens can lose functionality and molecules can degrade at different rates depending upon type and status of participant/donor and collection circumstances[2,3]. It is important to identify critical factors which predispose different specimens to deterioration and contamination (see *Section D3.6.3. Preanalytical Variation*). 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) 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/participant, 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[4]. Tissue specimens should be maintained at optimal temperatures, as specified by the collection protocol (see *J3.5. Specimen Temperature*). Consideration should be given to using appropriate storage solutions that will maintain the integrity of the specimen (*e.g.*, viability and vitality) during transportation to the repository. In general, specimens should be processed as rapidly as possible with minimal manipulation.

### J3.1. Identification and Labeling of Specimens

The ability to identify and locate specimens, as well as link them to their associated data, including their life cycle within the repository, is central to the function and purpose of a repository. The primary mechanism for this is through the use of specimen identifiers.

#### J3.1.1. Specimen Identifiers

Specimen identification, tracking, storage, and distribution requires a distinct, trackable specimen identifier (specimen ID) in the form of a number, alphanumeric characters, a code (barcode or QR code) or an electronic tag (*e.g.*, RFID). Specimen IDs can be affixed to a specimen container in the following ways:

- Adhesive label (printed by a label manufacturer or within the repository).
- Container-integrated, *e.g.*, 2D matrix codes imprinted on the underside and or side of a container).
- Written directly on the container, using ink designed to be durable under the intended storage conditions.
- Tied to the specimen or container (*e.g.*, for robust plant material).

Label placement and orientation on containers should be uniform and standardized when used, eliminating any deviations such as wrinkles and creases to avoid downstream difficulties with reading and/or scanning.

A specimen ID should be:

- Distinct with respect to the collection, repository, network, or end-users. Note that some key stakeholders and or end-users may need to account for previous studies/collections and specimens received from other organizations. Where feasible, it might be a globally unique Specimen ID[5].
- Persistent in the following ways:
  - » Follow the specimen regardless of container throughout the specimen life cycle within the repository and for distribution.
  - » Remain unchanged in the inventory management system (IMS; see *Section I3. Inventory Management System*).
  - » Physically appropriate for the storage equipment used including withstanding the environmental conditions (temperature, humidity, etc.) of the system.
- Human-readable or have a human-identifiable component in the case of code use. When using barcodes or other machine-readable systems, human-readable information should be included, especially for distribution to end-users without the capability to scan barcodes.

In many cases, specimen identifiers are generated according to criteria local to the repository that hosts the specimens. However, additional criteria as specified by applicable domain practices, or other stakeholders (*e.g.*, end-users, central collection, or consortia partners) for the container and specimen ID may be applicable.

***BEST PRACTICE:*** A specimen should be identifiable at each stage of its life cycle within the repository, regardless of format or container during each stage.

### J3.1.2. Specimen ID/Label Formats

A specimen identifier can be designed in a number of ways with or without incorporation of additional information.

**No additional information incorporated:** The specimen identifier is generated as a string of characters without specific meaning, other than as a means to identify the specimen. Of this, the most common type is sequential numbering. Use of this schema means that Specimen IDs are highly unlikely to change over the life cycle of the specimen. Repositories that support blinded or masked analysis by end-users (*i.e.*, to avoid research bias) may wish to consider using this scheme.

**Information incorporated within the specimen identifier:** Alternatively, design can incorporate information other than the specimen identifier. Depending on the repository type, information such as genus and species, clinical data, and code to track temporally distinct specimens from a participant/donor may be part of the identification and/or labeling schema. Information for administrative purposes, for IMS functionality, or both can also be conveyed.

**Information incorporated within the Label:** In some systems, the Specimen ID is printed onto a label and is accompanied by additional data or codes that are pertinent to the specimen, *e.g.*, international registry code such as ICD-10 (International Classification of Diseases 10th Revision), type of tissue and how it was collected, expiration date.

Protection of privacy and confidentiality, and compliance with applicable regulations and organizational policies (see *Section C2.1. Managing Research Risks for Participants*, and *C1.2.1. Compliance*), additionally applies to identification and labeling. To comply, the specimen ID and label information should not be derived from personal information of the donor/participant.

The specimen location should not be part of the label or specimen ID, as locations may change over time. Labeling by hand is generally not recommended, due to issues with legibility, permanency, and incompatibility with automation (see *J3.1.5. Specimen Identifiers/Labels and Automation*).

#### J3.1.2.1. Barcodes

Whenever possible, specimen ID should be denoted by a barcode that identifies the specimen, is machine readable, links to the IMS for the relevant specimen and its annotated data, and still retains a human-readable or -identifiable component. Barcodes can be 1 Dimensional (1D) standard barcodes, with lines of varying width in a straight line or 2D codes, typically known as quick response (QR) codes, normally presented as squares with smaller squares in specific sequences.

1D barcodes are limited to alphanumeric information, often a specimen ID, whereas 2D codes can contain significantly more information (date/time of scan, specimen type, images, etc.). Laser-etched 1D /2D pre-coded containers should be favored over adherent labels for specimen storage at ultra-low temperatures, especially when containers are handled or stored using automation systems.

While 2D barcode scanners can generally read both 1D and 2D barcodes, not all 1D barcode scanners can read 2D barcodes. Scanners that are specifically designed for 1D barcodes might not have the necessary hardware or software capabilities to decode 2D barcodes. Beyond single specimen vials, barcodes can also be used to track multiple specimens, as in the case of storage units such as vial containers and racks.

#### J3.1.2.2. RFID

Radio-frequency identification (RFID) tags can be used instead of or in addition to barcoded labels. These tags can be on specimen containers and/or in racks housing multiple containers. The identifier stored in the RFID tag should be linked to the IMS for the relevant specimen and its annotated data. RFID provides greater accuracy and speed when compared to barcodes or manual systems. With an RFID system in place, the tagged item can be easily located without having to manually scan each container/rack individually, as with a barcode system. While RFID enables real-time inventory management, implementation may be costly and time consuming. Challenges include the need to have power for the system, and possible interference from other electronic devices in the vicinity.

***BEST PRACTICE:*** The use of barcodes (*e.g.*, 1D, 2D QR codes) or RFID for the specimen identifier is highly recommended to ensure accurate tracking of specimens.



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### J3.1.3. Tracking and Traceability

Tracking helps to trace every aspect of the specimen's journey, from collection or acquisition through to distribution, transfer, or disposal throughout its life cycle, and enables the creation of a chain of custody. The specimen ID should be tracked using a database containing relevant specimen details (see *Section I3.2. Specimen Descriptors*).

Specimen relationships should be tracked to preserve any lineage, from the source specimen (sometimes referred to as the parent) to the aliquoted or divided derivative specimen(s) (child or children). This relationship can be reflected in a separate data field in the IMS or in the series used for the specimen ID numbering scheme in a way that demonstrates an association to the source specimen ID or both.

#### J3.1.3.1. Tracking of Loan, Legacy, or External Specimens

A repository in receipt of large numbers of legacy specimens should determine an optimal course of action for identification, tracking, and traceability going forward. Factors for consideration can include:

- Decipherability of existing specimen identifiers.
- The cost and potential impact on specimen integrity to apply new identifiers.
- The ability to track the legacy specimens within an IMS.

Any specimens loaned by another organization should already have a specimen ID, which can be used while on loan. If the specimen ID does not exist or is not workable, a temporary specimen ID should be assigned to enable traceability while in the receiving repository. Clear traceability should be maintained to any historic references (*e.g.*, through use of a label including the historic reference).

Repositories should consider the flexibility within their processes and systems (including any IMS) to incorporate any specimen IDs that typically come from other organizations (including loans, legacy, or external specimens for use within the receiving repository) that may have different or alternative identification formats (see *Section I3. Inventory Management System*).

***BEST PRACTICE:*** Each specimen in the repository should be traceable through the use of a specimen identifier. A specimen should also be traceable to all previous iterations and stages of the specimen and data.

***BEST PRACTICE:*** The repository's unique identifier for each specimen should be durably printed/marked on the label or container, and if labeled in barcode format (or machine readable such as RFIDs), human-readable information should be associated for readability and traceability outside of the repository.

***BEST PRACTICE:*** To minimize the risk of loss or misplacement of the specimen, the specimen should additionally be physically findable at each stage.

### J3.1.4. Specimen Identifier/Label Resilience

Specimen identification and labeling (including in-house generation of specimen IDs/label, where relevant) should be evaluated (see *Section D3.6. Validation, Verification, and Qualification*) under conditions as extreme as the anticipated processing and storage conditions before being put into regular use. A pre-approved test plan should address permanence, decipherability, and stability of the specimen identifier in the storage conditions used in the repository as well as known downstream applications (*e.g.*, heat blocks, water baths, xylene, alcohol). Where relevant, the ability to scan should be addressed. The barcoding and scanning software should be evaluated when integrated with the IMS.

When choosing or reviewing the method used for specimen identification, factors that may impair the readability or tracking should be addressed. Such factors might include the container material, exposure temperature(s), or the use of substances or solvents that degrade labels and ink.

***BEST PRACTICE:*** The type of specimen ID/label should be evaluated for its performance over a variety of conditions prior to use.

### J3.1.5. Specimen Identifiers/Labels and Automation

One of the first steps in considering automation within a repository should be the labware type utilized. While the choice of labware is optional, automation manufacturers may recommend limited formats, manufacturers, and/or suppliers. The labware selected should be validated and verified for the conditions of automated handling, picking, and/or storage (see *Section D3.6. Validation, Verification, and Qualification*). At a minimum for automated storage, a specimen identifier that can be read electronically (barcode, RFID, etc.) should be on each

specimen container. Generally, picking and storage processes can only be automated if the specimen containers have a barcode label. Containers or vials with pre-affixed specimen IDs, etched on the container and/or 2-D bottom-barcoded on the side or QR coded on the bottom, are recommended. Although this may be a more expensive option, legacy collections without scannable codes or tags are not considered automation friendly. Hand labeling and physically applied labels are not recommended as these are not compatible with automation given issues with legibility, permanency, and inability to scan. However, depending on the automation selected, it may be possible to use container adapters compatible with the automation format. Such adaptors should be equipped with a scannable code or tag to enable tracking and identification of the specimen within. If transitioning to automation for storage, the repository should be aware of the need to evaluate existing and new labware and specimen identification systems and devise workable strategies. Resources required might include additional upfront costs for automation-friendly labware and an investment of personnel time to assess and determine solutions to adapt and/or handle any existing specimen containers within an automated system.

## J3.2. Sterility and Cleanliness

Risk assessments and mitigation planning (see *Section B1.4. Assessment, Control, and Monitoring of Risks*) should be undertaken in the context of the requirements for specimen asepticity and stability. While completely 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. Microbial/viral/parasitic contamination can potentially affect specimen stability through accelerated degradation of specimens potentially affecting specimen stability before storage or during cooling or warming. 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 supplies such as liquid nitrogen should also be considered.

## J3.3. Specimen Containers

Collection and storage primary containers (*i.e.*, those directly in contact with the specimen) vary according to specimen types being collected, the temperature of the intended storage, and the analytical goals of the research. During selection of container type, consideration should be given to the long-term use, standardization, and applicability to any existing and potential new platforms, such as automation (see *Section H4. Automated Storage Systems*). Not all containers used for specimen collection are suitable for all conditions of specimen storage.

The specimen container and cap (or other closure system) have the potential to impact significantly on specimen integrity, as well as costs associated with purchasing, storage, and transport among others. To prevent cracking due to extreme temperature exposure, specimen vials or containers and caps should be made of a high-grade durable material, designed to prevent leachability of products into the specimens, evaporation, and degradation under handling and storage conditions.

In some cases, contaminants associated with the container and caps (*e.g.*, persistent organic pollutants, phthalates/plasticizers, heavy and trace metals) may interfere with subsequent analysis. This issue is especially true for specimens stored for environmental analysis. Container and caps composition should also be resistant to the chemical nature of the specimens and/or media. They should be compatible with any preservatives used. Liquid nitrogen has an expansion ratio of 1:696 when brought from a liquid to a gaseous phase at room temperature. When removed from cold storage, glass, metal, and some plastic specimen containers (*e.g.*, vials, tubes, straws) can crack and/or explode if liquid nitrogen ($LN_2$) is trapped inside the specimen container. Certain containers, like cryogenic straws, are hermetically sealed and specifically designed for the safe storage of specimens in the liquid phase of nitrogen.

Oversized containers negatively impact inventory storage space and can increase associated transport costs (see *J8. Specimen Inventory Management*). A large container dead-space volume to specimen volume can alter pH. Therefore, when considering the optimal specimen container size, it might be necessary to balance between the volume to account for expansion of frozen specimens without entry into the cap and use of an oversized specimen container. The repository may additionally consider any criteria associated with robotic liquid-handling systems and automated storage, in particular, compatibility with picking, scanning, and storage systems.


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### Vials and Caps

Many vial configurations with similar diameters ranging in size from 0.2 to 5 mL volumes are available. Factors important for cap choice (screw caps, flip caps, pop-in caps, etc.) include cap profile height, ease of use, suitability for use in different applications (*e.g.*, high pressure environments, automation), closure integrity, and contamination risks.

Screw-cap vials may have internal or external threads. Vials and caps not made of the same material are likely to respond differently to temperature changes. This can result in gaps, potential leaks, and subsequent specimen contamination during submersion of screw-capped vials in the liquid phase of nitrogen. However, such vials and caps may be validated for use in liquid nitrogen vapor phase (LNVP), where relevant. Flip and pop-in caps can work well for some applications (*e.g.*, to maximize inventory storage space and minimize shipping costs) when housed in boxes that enable a tight configuration (*i.e.*, the box lid gently presses down on the vial lids). However, dexterity of use (*i.e.*, additional devices are necessary for pop caps use), and use in $LN_2$ or with automation may be compromised.

To prevent specimen contamination by $LN_2$ (see *Section F4.1.1. Biosafety*), it is recommended to use hermetically sealed, high-quality containers and/or a secondary sleeve enclosure (*e.g.*, bag or straw in straw) capable of preventing passage of gasses and liquids[6].

### Bags

Cell freezing bags or cryobags, a technology borrowed from the blood banking industry, is the container of choice for most cell therapy preservation due to the available infrastructure for processing, freezing, and storage of these container systems. Blood bags are available in a wide range of volumes, with most utility being in volumes larger than 5 mL. While smaller-volume bags are available, complete specimen withdraw can become challenging. Cell freezing bags can be configured in any number of ways with off-the-shelf ports and tubing sets, allowing flexibility to customize around filling and retrieval processes. These bags are also available with unique serial numbers which are reproduced on integral tubing to allow test segment production and identification for future testing of the product.

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 specimens are taken from extreme environments (*e.g.*, cryogenic temperatures, heat shock) (see *J3.1. Identification and Labeling of Specimens*). Light-sensitive specimens should be stored in containers that do not allow penetration of light such as amber vials or amber-coated bags (see *Section G4.2. Task Lighting*).

It is important that specimen container type selection should be extensively assessed prior to purchase and evaluated prior to use (see *Section D3.6. Validation, Verification, and Qualification*).

***BEST PRACTICE:*** Specimen containers and caps selected for storage should be tested according to planned use prior to use.

## J3.4. Specimen Stability

Specimen stability can be affected by a variety of parameters such as the use of anticoagulants and stabilizing agents like ethylene diamine tetraacetic acid (EDTA) in blood and ascorbate in urine[7,8]. Instability can manifest as an undetected problem in an individual specimen or can result in a more general effect between repositories using different methods. As deleterious impacts to stability are generally invisible, it is important to understand any criteria (*e.g.*, manufacturer assay kits) that can impact on stability relevant to fitness for purpose (see *Section D1. General Introduction to Quality Management*). For some applications, rapid dehydration and freezing are effective methods to stabilize molecules (see *J3.7. Specimen Preservation*). Dehydration methods may be more practical in field settings where access to refrigerants or chemical fixatives is dangerous, cumbersome, or not feasible. Multiple freeze thaw cycles can adversely affect specimen stability and should be avoided, where practicable (see *J3.8. Freeze/Thaw and Cooling/Warming Cycles*).

Specimen stability can also be 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. An important variability factor in pre-analytical procedures is time and includes collection time, processing time, or long-term storage time as well as relevant delays during collection and processing stages. The impact of these times can be assessed by short- or long-term stability studies[9].

Recording of processes and activities that specimens undergo facilitates the assessment of fitness for purpose. The standardized tool Standard PREanalytical Code (SPREC) (*e.g.*, for body fluids)[10] can assist with this.

***BEST PRACTICE:*** Selected methods for collecting and preserving and or storing specimens should be followed to ensure that any preservatives, dehydration, or other protective treatments used do not have a deleterious effect on fitness for purpose.

## J3.5. Specimen Temperature

Because cold preservation is a critical stabilizing factor for many specimen types, the temperature ranges at which specimens are collected, processed, stored, and distributed should be carefully considered and documented[11,12]. Stakeholders such as end-users may also define temperature parameters to be followed. These may range from chilling/hypothermic (2 °C to 8 °C) to low subzero (0 °C to -4 °C) or 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).

Specimens can also be collected, shipped, and stored at ambient temperatures using technologies that have been developed specifically for such purposes (see *Section H7. Ambient Temperature Storage*). Ambient preservation can be used for purified analytes (DNA and RNA)[13] 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, decades[14]. Technology for preserving dried blood spots (DBS) on cellulose-based cards/filter papers at ambient temperature has been well described for human specimens in literature, particularly for global health diagnostics and surveillance programs[15]. It is also described for use in the animal domain with additional reference to its use for fluids other than blood, such as urine, milk, and saliva, known collectively as dried matrix spots[16,17]. Humidity can be a concern when using ambient storage (see *Section H7.1. Humidity Monitoring*).

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 recommended to maintain appropriate temperature ranges from the point of collection or acquisition 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, ambient temperature is recommended. Consideration of downstream assays is critical, as hypothermic conditions may induce changes in specimen 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 specimens collected to yield serum are often maintained at room temperature to facilitate 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). The occurrence of fibrin may result in clots in thawed aliquots which can impede pipetting assays and therefore should be documented when encountered.

Where low and ultra-low temperatures are desirable to maintain integrity of a specimen type, all stages of the specimen life cycle should be continuously coordinated using temperature-controlled environments for cold chain management (see *Section L5. Cold Chain*). Temperature exposures, in particular out of range events, for each stage of the specimen life cycle should be recorded, documented, and available for reporting as part of quality control results (see *Section D3.5. Quality Control Approaches*).

***BEST PRACTICE:*** Continuity of the cold chain should be maintained and documented for all specimen life cycle stages.

## J3.6. Specimen Integrity Monitoring

The physical and functional integrity of the specimen is dependent on the maintenance of the correct storage conditions. A comprehensive monitoring system should be implemented within the facility to alert personnel to changes in parameters affecting specimen integrity that require a prompt response to prevent specimen loss or damage (see *Section H10. Environmental Monitoring Systems*). This system should monitor specimen storage conditions (*i.e.*, temperature) and functionality of storage equipment and essential services (*e.g.*, $LN_2$ consumption, power) to mitigate the risk of storage malfunction or failure (see *Section H2.2. Monitoring Liquid Nitrogen Storage Parameters* and *H2.3. Detecting Liquid Nitrogen Storage Equipment Failure*). The monitoring system should include multiple redundant sources of both human and electronic components to avoid unintended failures, including safeguarding mechanisms to prevent inadvertent disarming of the alarm/alert system (see *Section B1.4. Assessment, Control, and Monitoring of Risks*, Table B1. Repository Risk Categories and Proposed Mitigations). Storage units suspected of imminent failure or near to or at the end of their serviceable life should be taken out of service. Where this is not feasible, a level of monitoring commensurate with the risk of failure and the importance or rarity of the stored specimens (see *Section H12.2. Repair or Replacement*).



ISBER Head Office: 1618 Station Street, Vancouver, BC, V6A 1B6, Canada
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## J3.7. Specimen Preservation

Preservation is a general term used to describe the process of using a variety of fixation/preparation techniques and a range of low temperatures or ambient storage methods to preserve biological materials of all types (*e.g.*, living cells, tissues, fluids, organs, organisms). 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.

### J3.7.1. Preservation Techniques

Common methods of preservation (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 within paraffin, creating a Formalin-Fixed Paraffin-Embedded (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). While fresh tissue is considered optimal for processing into FFPE blocks (particularly for histology, immunohistochemistry, and morphology characterization), frozen-thawed specimens can be used for some purposes (*e.g.*, molecular analysis) if it represents the only available specimen or where a need exists to convert archived specimens. Standardization and optimization of pre-analytical variables are critical regardless of the specimen source. Factors such as freezing method, storage conditions, and thawing protocols need to be carefully controlled and documented to minimize potential artifacts and ensure reliable results. The details (*e.g.*, time and protocol) of this conversion should be documented, to help determine any impact on fitness for purpose.

Another common clinical technique is preservation of dry blood spots on paper or other matrices. Once dried, the specimen's nucleic acids, metabolites, and proteins could be stable for months to years at ambient temperature or under refrigeration. Other methods include concentration and preservation of fluid specimens on a dry matrix (*e.g.*, dry concentrate of urine or its components on a membrane), freeze drying (lyophilization), foam drying, and spray drying. Technical improvements in these methods offer potential to further unlock improved preservation alternatives to cryopreservation for a wider variety of specimen types[18].

### J3.7.2. Cryopreservation Techniques

Cryopreservation involves the process of cooling specimens to preserve structure and function[19]. If cooled below -136 °C (the glass transition point of pure water) all biological activity, including the biochemical reactions that lead to cell death, are stopped. This allows for indefinite storage, as long as such temperatures are maintained.

There are two distinct types of cryopreservation:

- Preservation in the frozen state (*i.e.*, in the presence of ice crystals).
- Preservation in a glassy, non-crystalline state in the absence of ice (*i.e.*, vitrification).

Preservation in the frozen state may be divided into:

- Uncontrolled cooling (*i.e.*, direct exposure to $LN_2$ or another cryogen) known as snap-freezing or ultra-rapid cooling where no attempt is made to control the presence or location of ice in the system.
- Controlled-rate (or equilibrium) cooling by either active (programmed) control or through passive cooling. Here, control of the location and quantity of ice in the system is important.

The choice of cooling method depends on the purpose for which the specimen is being preserved. In general, snap-freezing is used where preservation of cellular components or biological macromolecules is the primary aim. In contrast, controlled-rate cooling is used when the main aim is to preserve biological function.

When cooling is applied, extracellular ice formation is controlled through nucleation. Nucleation will occur either randomly, or by intentional "seeding" of the extracellular space. Applying a slow cooling rate gives time for water to leave the tissue, cells, or organisms during the progressive freezing of the extracellular fluid, thereby reducing the likelihood of intracellular ice formation. Application of cryoprotectants, such as dimethyl sulfoxide (DMSO), is recommended to minimize or circumvent cryoinjury caused by damaging cell volume changes and the excessive concentration of solutes. Cryoprotectant additives (CPAs) are compounds that provide protection to the specimens being cryopreserved through a variety of different mechanisms.

During controlled-rate cooling a number of physical parameters should be controlled to optimize cellular recovery. These are the:

- Cooling rate.
- Extracellular ice nucleation temperature (or seeding temperature).
- Sub-zero temperature at which specimens are transferred to LNVP or $LN_2$ storage.
- Hold time at the sub-zero transfer temperature.
- CPA addition rate and concentration.

**Cooling Rate:** The optimal cooling rate for cell recovery is dependent on cell size, cell membrane permeability to water and the CPA type and concentration, the surface area to volume ratio of the specimen, and its geometry. For many types of cells, a cooling rate of around 1 °C/minute is appropriate. This may be achieved using commercially available programmable, controlled-rate freezers (either electrically driven or $LN_2$-fed) or alcohol-based (or alcohol-free) bench-top, passive, cooling devices.[20]

**Ice nucleation temperature:** In the initial stages of cooling, specimens cool below their freezing point (termed supercooling or undercooling). The degree of supercooling can be highly variable, leading to specimen-to-specimen variation in post-thaw viability. Ice nucleation, following a significant degree of supercooling, can lead to rapid ice crystallization and the formation of potentially damaging intracellular ice. Nucleation is an exothermic reaction and the latent heat released as ice forms can also indirectly affect cooling rate. The latent heat generated causes an increase in the temperature of the specimen at a time when external cooling is still being applied. This creates a temperature differential between the specimen and its external surroundings which, once latent heat is removed, can lead to rapid, sub-optimal cooling of the specimen. The degree of supercooling can be controlled by inducing ice nucleation (seeding) by a number of methods (*e.g.*, application of ice, vibration, or ice nucleating compounds). Adding a sub-zero hold period into the controlled rate cooling program allows the release of latent heat of fusion and prevents uncontrolled specimen cooling.

**Transfer temperature**: Damage during cooling generally occurs at temperatures down to around -50 °C and therefore transfer to long-term storage should not be initiated before -50 °C is reached. To better avoid exposure to potentially damaging temperature rises during transfer, controlled-rate cooling should be continued to at least -80 °C before specimens are transferred to storage. Furthermore, the transfer temperature should be determined based on the stability of the specimens being transferred[21].

**Holding time:** During cooling, specimen temperature lags behind the temperature of the cooling device or controlled-rate freezer. Once the device reaches its predetermined transfer temperature, specimens should be allowed time to thermally equilibrate before transfer to long-term storage.

Vitrification is an alternative form of preservation at ultra-low temperatures where the specimen is cooled without the formation of ice crystals. An increase in the viscosity of the cells' intracellular water coupled with rapid cooling induces a glassy or vitreous state. This can be achieved by:

- Ultrarapid cooling of specimens in low, non-toxic concentrations of a CPA. However, this can lead to an unstable glass that is prone to devitrification and ice crystal growth if the specimen is inappropriately warmed. Due to the ultrarapid cooling rates needed to achieve vitrification, specimen size is generally very restricted.
- Slow cooling of specimens in high (normally toxic) concentrations of CPAs. The addition of CPAs at high concentrations increases the viscosity of the aqueous solutions (intra- and extracellular) in the specimen and prevents ice crystals from forming. The result is a stable glass that allows for larger size specimens to be vitrified at achievable slower cooling rates. CPA toxicity can be mitigated by using combinations of CPAs, each at a low concentration, or by sequential addition of increasingly higher concentrations of the CPA at increasingly lower sub-zero temperatures.

**Use of CPAs**: Both types of cryopreservation generally require the addition of CPAs. CPAs are applied in different regimens, combinations, and concentrations depending upon the specimen being preserved and the type of cryopreservation employed. Common CPAs, such as glycerol, DMSO, ethylene glycol, or propanediol are often toxic in high concentrations. When possible, the repository should test available preservation solutions to optimize post-thaw viability and vitality (including retention of function; see *Section D3.5.3. QC for Cells, Viability, and Vitality*) and, as required, to pilot test the CPA for the specific specimen. Using an appropriate cryopreservation medium and CPA reduces the rate of degradation at hypothermic temperatures and offsets risks of inadvertent devitrification when the specimen is at ultra-low temperatures.


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The temperature at which cryopreserved specimens are stored can affect the length of time the specimen can be stored before its viability is affected. As temperature is reduced, metabolic and degradation processes in cells are slowed resulting in long-term stability[22]. For vitrification solutions, the actual Tg may need to be determined using thermal analyses (*e.g.*, differential scanning calorimetry) to determine the optimal storage temperature.

### J3.8. Freeze/Thaw and Cooling/Warming Cycles

The biggest contributor to unintended specimen transient warming is inventory management practices. Opening and closing storage units to add/retrieve materials, to verify inventory, or for transfer to another storage unit can be frequent and are often not considered equivalent to a major event such as a storage unit failure but can have a similar effect depending on the frequency of such events over the life cycle of a specimen. Cooling/warming cycles for specimens can be damaging to specimen macromolecules and cells intended for analysis. Damage due to accumulation of osmotic and dehydration injury can also occur during CPA exposure and removal and vitrification treatments. The number of deliberate cooling/warming (freeze/thaw) cycles and unintended transient warming events should therefore be minimized. Determining specimen aliquot volumes/sizes that are appropriate for distribution and the intended uses of the specimens can help minimize the number of times a specimen is thawed and refrozen or vitrified before use.

The primary aim with cell and tissue preservation is to maintain specimen stability. However, during normal operation, the temperature within the storage vessel fluctuates (as liquid nitrogen is consumed and replaced or in mechanical freezers with door opening and closing). This may result in specimen temperatures repeatedly cycling through the Tg even while remaining in a sub-zero frozen state. Vitrified specimens particularly prone to devitrification should therefore be stored at locations in the storage vessel where temperature fluctuations are minimal.

In addition to storage temperature, handling during removal from storage affects the viability of cells and may result in degradation of cellular components. For instance, during retrieval of a stored specimen, adjacent specimens may experience a temperature rise. Every time a specimen is warmed above Tg, it experiences a destabilization event. Repeated thermal cycling may lead to increased cell death via apoptosis and necrosis. It is essential therefore to avoid or limit thermal cycling when specimens are introduced or removed from storage as well as during transport or shipping.

Delayed-onset cell death resulting from preservation stress may affect the quality of data obtained from specimens depending on the timing of experiments post-preservation and the ability of the cells to recover from cryoinjury over time.

***BEST PRACTICE:*** The number of cooling/warming (freeze/thaw) cycles of a specimen should be minimized and any such occurrences documented.

## J4. COLLECTION CONSIDERATIONS

A variety of protocols exist for the collection of different specimen types. The welfare of the participant or donor should be of primary concern in the execution of these protocols (see *Section C. Ethical, Legal, and Social Implications*). Specimen types, sources, and numbers of individuals for collection are influenced by a number of factors including:

- Fitness for purpose.
- Ethical and legal implications: Including ethical approvals, consent, permits, and legal agreements as relevant.
- Volume/amount to be collected: For example, collecting multiple specimen types from a single organism to compare the concentration of an analyte across different specimen types at different time points, *e.g.*, urine versus blood.
- Resources available, *e.g.*, costs, expertise, access.
- Ease of collection: For instance, collecting specimens from animals may be challenging depending on size and physiology, and temper/aggressivity. Tissues may be collected post-surgery or post-mortem[23]; bodily fluids may be collected from participants, and environmental samples may be site specific and require additional local assistance.
- Traits of the species or cells for selection, particularly for detection of the presence or absence of specific organisms or for further culturing.

The chosen protocol should therefore be suited to the repository's particular needs, specimen types to be collected, the collection's geographical locations (*e.g.*, field, laboratory or clinical settings), and intended purpose. Some specimen collection considerations are presented herein. Protocols for the field collection of non-human specimens are often highly taxon-specific, and further guidelines for major eukaryotic taxonomic groups may be found in Gemeinholzer *et al.*[24] and more recent FAO animal and plant guidelines[25,26]. A seminal publication on biodiversity biobanking protocols and practices provides recommendations and is additionally a resource to other relevant publications[27], (see *Section D4.2. Guidelines*).

Efforts should be made to avoid participant/donor and specimen contamination as necessary, *e.g.,* disinfection of instruments and glove changes. The collection method should be documented. Collection or sampling records should be maintained and tracked including for the time elapsed between the relevant specimen life cycle stages (collection, processing, preservation, storage). Date and time stamps can be used to maintain these records efficiently (see *Section D3.2.1. Creation of Documented Information*). All relevant accompanying data, including images taken, should be documented (see *Sections D3.2. Documentation Management and Control*). Specimen collection containers should be pre-labeled with specimen ID, particularly for high-volume collections, to improve workflow and ensure accurate labeling and specimen tracking (see *J3.1. Identification and Labeling of Specimens*). When a repository does not directly conduct collections but otherwise acquires or accessions specimens and associated data, the following needs to be considered:

- Use of agreements (see *Section K3. Transfer Agreements*) to stipulate any requirements (*e.g.*, legal, ethical, and biosafety); see *Section F4.1. Biorisk Management*.
- Procedures used for the collection process (these can be predefined with the repository or not).
- Quality control on incoming specimens and associated data (*e.g.*, to prevent contamination of existing collections; see *Section D3.5. Quality Control Approaches*).

***BEST PRACTICE:*** Collection of human and animal specimens should never interfere with patient diagnosis or clinical care.

***BEST PRACTICE:*** The repository should ascertain the need for ethical review and approval by an appropriate ethics committee and undertake this where necessary along with any legal obligations (*e.g.,* permits) prior to collection (see *Section C1.3. Ethical Review*).

***BEST PRACTICE:*** Collecting from animals should take into account the security and welfare of the subject, as well as the safety of the personnel.

***BEST PRACTICE:*** Field collecting (*e.g.*, for biodiversity) should not threaten a species' or population's existence.

## J4.1. Liquid without Cells

While this content generally pertains to liquid specimens without cells, it should be noted that some liquid specimens may in fact contain small numbers of cells[28].

### J4.1.1. Urine

As a specimen, urine can help inform on the status of kidney function or as an ultrafiltrate of plasma to help study homeostasis and metabolic processes. Usually sterile[29], sufficient volumes are generally possible by non-invasive collection with relative ease. Collection containers should be sterile, dry, have sufficient capacity relative to the participant/donor, a wide opening, and a leak-proof cap. A preservative (*e.g.*, EDTA, acidification, and sodium metabisulfite), may be needed, depending upon the purpose (*e.g.*, the analyte to be measured). The type of preservative may differ according to test methodologies, time delay, and transport conditions. Urine containers used for environmental toxicology assays should additionally be consistent with protocol requirements (*i.e.*, prescreened for phthalate metabolites). Specimens should be maintained on wet ice or refrigerated after collection prior to processing. Urine can be centrifuged to remove cells and debris resulting in acellular urine and a cell pellet for use or storage as aliquots. Condensed urine on filters may be an alternative approach for difficult to collect specimens, *e.g.,* in neonates[30]. Many urine collection methods used for human[31] and animal species[32] are dependent on the intended purpose. Collection procedures should specify the time (*e.g.*, random, first morning, timed, other), and type of collection (*e.g.*, fractional, midstream). Fractional specimens can be used to compare an analyte concentration in urine versus blood; first-morning urine is discarded. Following a determined period, a specimen is collected from the next urination event. A midstream or clean-catch (the participant/donor starts urinating and then the collection container is positioned in the stream of urine) can be conducted at any time. Cleansing the surrounding skin prior to collection can result in reduced cellular and microbial contamination.

### J4.1.2. Milk

The milk collection procedure should address the type of milk to be collected (*e.g.*, colostrum, foremilk, hind milk). For colostrum (an important immunological booster for the neonate), it is advised to collect a minimum volume on the first day of breast-feeding or suckling[33]. While milk collection can be initiated when breast-feeding/suckling starts, the procedure may need to address the timing of the milk specimen relative to both the time of day and days postpartum. Breast milk can be collected by manual expression or vacuum pump and should be collected in sterile or specially-cleaned bottles. A guidance for industry produced by the US Food and Drug Administration, Clinical Lactation Studies: Considerations for Study Design[34] can be consulted for relevance.


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#### J4.1.3. Miscellaneous Fluids

Other body fluids are collected for microbiological or clinical laboratory testing as part of the diagnosis and management of a variety of diseases. Most (*e.g.*, pleural, peritoneal, pericardial) are collected by ultrasound-guided aspiration, while other collections (*e.g.*, synovial fluid, amniotic fluid) may require visually-guided needle aspiration.

Collection devices for oral fluid 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). Saliva 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 centrifuged, which results in supernatant and pellet aliquots which can then be analyzed and/or stored separately. Buccal cells may be useful as a source of DNA. A variety of collection techniques and containers have been developed specifically for these collections[35].

Throat swabs and washes are collected primarily for research of Group A *Streptococcus* and *M. tuberculosis*. Nasopharyngeal swabs and washes are collected primarily for research of the nasopharyngeal microbiome, including respiratory viruses.

### J4.2. Liquid with Cells

#### J4.2.1. Blood

The collection of blood should be performed according to a fit for purpose procedure that takes into account specific constraints of the collection (*e.g.*, geographic distances between collection and processing sites, low resource setting). Collection should account for downstream intended or potential use especially for cellular, metabolic, and/or genomic analyses; these may require unique collection tubes, processing procedures, and storage conditions that should be determined before blood collection.

One of the primary considerations in blood specimen collection is what to collect[36]. Preparations can include:

- Whole blood: typically collected using anticoagulants without centrifugation so that all constituents are present.
- Anticoagulated blood: coagulation is hindered and centrifugation produces plasma (containing clotting factors), buffy coat, peripheral blood mononuclear cells, red blood cells). Blood collected with an anticoagulant can yield a packed cell volume to be used as a source of RNA or DNA (from the buffy coat layer), or viable cells. It is important to determine which anticoagulants are acceptable for downstream applications (see *J3.4. Specimen Stability*).
- Coagulated blood: results in a clot, and serum without blood cells and clotting factors). 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.

Existing phlebotomy guidelines[37], including a priority order of draw when multiple blood collection devices/containers are involved can be consulted. Where the order of draw differs, the specified procedure should be followed and the draw order documented. Blood collection procedures should account for any preanalytical factors that might affect specimen integrity negatively affecting fitness for purpose[36]. Such factors can include temperature, time, and transport format (*e.g.*, manual transfer, pneumatic tube, shipping) (see *Section D3.5.2. QC for Fluid Specimens*). For example, cell viability and functionality in blood specimens may be compromised during extended ambient storage/transport.

Viable cells from blood specimens including erythrocytes, granulocytes, leukocytes, etc., can be cryopreserved and stored at -80 °C or preferably below -150 °C in LNVP (see *J3.7.2. Cryopreservation*). Hypothermic temperatures (2 – 8 °C) may extend stability of red blood cells, and spotting onto filter paper with drying can provide extended storage as well as the ability to ship immunoglobulin and DNA specimens at ambient temperature.

Additionally, arterial and venous cord blood can be obtained from delivered placentas and used for measuring blood gasses or cryopreserved and stored as a source of undifferentiated stem cells.

***BEST PRACTICE:*** Blood specimens should be collected, processed, and stored according to the manufacturer's specifications for the blood collection tube, and within one to 24 hours of draw, depending on the analytical endpoints.

***BEST PRACTICE:*** The procedure for blood collection should be fit for purpose and considerations should be made for collection and transport constraints.

### J4.2.2. Genital Tract

Genital tract specimens may be collected for multiple purposes such as detection of sexually transmitted diseases or fertility studies. These specimens could be vaginal discharge or lavages, semen, oocytes, and embryos. Where the semen yield per ejaculate specimen is anticipated to be low the repository may wish to collect other specimen types, such as blood, to enable genomic analysis, health assays, etc.

Liquid-based cytology is used for human cervical or gynecological cell specimen collection using a small brush (similar to a conventional smear test) deposited into a small container of preservative liquid (rather than being transferred directly to a microscope slide as for smears)[38]. Cervical vaginal lavages (CVL) can be obtained and used for diagnostic research. CVL should be collected in one container, transported to the laboratory on wet ice within one hour of collection, vortexed gently, and aliquoted according to the designated protocol. Vaginal discharge is manually captured with an appropriate sterile container; caution should be taken to avoid external contaminants.

Oocytes and in vivo embryo collections can be quite labor intensive depending on the species. However, procedures are well established to preserve female germplasm or tissues[39]. Generally, females need to be super-stimulated to mature the eggs and provide sufficient oocytes for future reproductive studies or species preservation. Collected oocytes can be used with selected semen for in vitro production of embryos containing the full species genome to be preserved. Stem cells can additionally be isolated from ovaries, cultured, and cryopreserved. The expertise of a team, the feasibility of reconstitution, as well as the costs of harvesting and collection can factor into the choice of collection strategy.

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. Seminal fluid is collected in a warm (20 – 40 °C), clean, dry, wide-mouth container and should be transported to the repository within an hour of collection.

Different techniques can be considered for collection from animals, depending on the animal, breed/line, and level of interaction. These include use of an artificial vagina, electroejaculation, pharmacological/manual massage of the accessory sex glands, or epididymal aspiration (exposed through a scrotal incision of a castrated or recently deceased animal), among others. Protocols for estrous synchronization may be used in females to optimize the libido of the male. Collection methods may need to account for specific species' effects concerning sperm cell fragility. Environmental conditions may influence the quality of sperm cells. Some species are seasonal, so semen production of the animal is optimal during a specific period in the year. Semen quality analysis (viability, morphology, motility, and concentration) after collection is important (see *Section D3.5. Quality Control Approaches*). The quantity of sperm cells needed may depend on factors such as species fertility, offspring yield per parturition, or assay to be performed upon distribution to the end-user. Epididymides can be collected from castrated or dead animals and shipped to the repository to collect matured epididymal sperm cells (see *Section L. Packaging and Shipping*).

## J4.3. Solid Specimens

### J4.3.1. Solid Tissue

The appropriate handling of clinical tissues procured for research purposes should always be facilitated by having a practicing pathologist or equivalent medical professional supervise the procurement; this is especially important to prevent compromising diagnostic specimens[40]. Tissue specimens are heterogeneous with respect to the percent tumor, normal, necrosis, and fibrosis[23]. 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 as associated data. Where possible, multiple sections or specimens (aliquots) should be created to ensure the entire use of the tissue or organ. 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 (see *Section H7.2. Storage of FFPE Tissue Blocks and Slides*).

### J4.3.2. Surgical Specimens

Remnant clinical specimens may be collected from diagnostic surgical procedures. Policies documenting the subset of surgical specimens exempt from pathologic review are in place at most hospitals, including veterinary hospitals[41,42]. If the specimen in question is not exempt, it must arrive at the pathology lab intact for examination


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before research samples can be procured. Any exceptions should be approved by the pathologist. The pathologist should also approve any exceptions in advance of tissue collection (either direct from current surgical specimens or indirect from specimens, such as FFPE blocks, stored by the hospital)[40].

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 important to prevent cross-contamination, 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. Few research protocols specify a need for sterility during procurement; however, where sterility is recommended, suitable clean area(s) to facilitate aseptic procurement and processing may need to be set up.

During specimen procurement, contact between different specimens should be avoided to prevent specimen contamination, and equipment used for procurement should be replaced between use on 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 the compromising of subsequent analyses, specimens should not be resected on a dry towel or other absorbent material.

Specimens requiring snap-freezing or flash freezing (cooling at sufficiently high rates to limit damage to cell structure; see *J3.7.2. Cryopreservation*) can be frozen in a Dewar of liquid nitrogen or on dry ice with ethanol at the time of collection. Where specimen morphology but not the 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.

***BEST PRACTICE:*** All personnel who collect tissue specimens (*e.g.*, surgeons, nurses, pathologists, repository personnel) should be trained and competent including in the specific handling requirements of each protocol.

***BEST PRACTICE:*** The collection of remnant specimens from medical procedures or clinical archives should be approved by a pathologist.

### J4.3.3. Post-Mortem Specimens

Remnant specimens may be collected from autopsy/necropsy procedures consistent with relevant regulations and protocols for diagnostic research. Requests for specimens should specify a maximum time interval post-mortem prior to processing. Autopsy/necropsy procedures may yield non-diseased, normal tissues or large quantities of a specimen that would not otherwise be available from surgical procedures (*e.g.*, heart, brain).

Tissue specimens collected post-mortem should be appropriately labeled for the organ site, tissue type, and time of resection (see *Section D3.2.1. Creation of Documented Information* for information on time and date format), and then placed immediately into a container of cold preservation media (2 – 8 °C) on wet ice. These organs or large tissues can be dissected into smaller sections for processing and storage. Detailed information about the deceased should be recorded such as disease condition, age, sex, race/species, 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.

### J4.3.4. Organs

All organs/tissues intended for research should be maintained in appropriate preservation media at 2 – 8 °C until processed, depending on the organ and the intended purpose. Isotonic saline or culture media may not be considered optimal for hypothermic preservation of viable cells/tissues/organs. Specific perfusion techniques can be applied to organs, such as the liver, to enable the 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, clot formation within the vasculature obstructs the penetration of the preservation solution into the tissue. This can result in tissue specimens that are not homogeneously preserved, and potential localized tissue damage due to ischemia. These changes may result in the tissue section being less representative of its original resected state. Transplant organs may be dissected into smaller sections during processing and storage.

### J4.3.5. Nails, Hair, Pelages, and Feces

Human nail and hair clippings can be used for trace metal and metabolite analysis to provide a long-term measure of exposure. They can also be used as a source of DNA. These specimens can be relatively simple to collect, store, and ship. Hair follicles may be used for molecular analysis.

For animal collections, non-invasive collection methods are increasingly used to reduce or eliminate stress resulting from invasive sampling. These can be preferred for breeds and populations that are endangered and/or that need specialist expertise. These methods can be applied to free-ranging and domestic or farmed animals, particularly for collections of molted or shed external layer(s), including skin; pelages such as hair, feathers, fur, and wool; keratin, including hooves and nails; and fecal matter. However, these non-invasive collection protocols need to take a number of factors into account, including:

- Possible contamination with pelage belonging to another animal (*e.g.*, with other individual's materials or decomposing microorganisms).
- The need to definitively identify and authenticate a specimen source where a variety of species with similar somatic features can frequent the same habitat.
- The collected material may not yield sufficient genetic material for some genomic analyses.

Human fecal specimens can be self-collected by participants into a container lined with plastic wrap or placed inside another container and then frozen. To avoid bias during sampling and transport, it is recommended to provide clear instructions and to follow up with the participant to ensure correct handling. When preserving at room temperature or when maintenance of cold chain temperature is challenging, a stabilizer (*e.g.*, preservatives such as ethanol or commercially available solutions) can be used (rather than plastic wrap) to avoid microbiome alterations and to minimize variability between specimens. Fitness for purpose may be a key consideration in the selection of preservative method as different preservative solutions can create bias in microbial communities in the specimens collected[43]. For non-wild/roaming animals, specimens are generally collected in the field or a containment cage. Some procedures will allow for lyophilizing the specimens for long-term storage, providing more inert (less odoriferous) and condensed specimens.

Considerations for fecal collection procedures may need to reflect an awareness of the variation that can occur both within a specimen and between specimens collected from different bowel movements, and the impact of time, temperature, and container on downstream applications.

### J4.3.6. Microbial and Protist Specimens

Common microbial collection methods include swabbing, air sampling, water filtration, and soil core sampling. Measures should be taken during collection (*e.g.*, use of appropriate temperatures, preservation solutions, and timely transfer to repository) to retain viability where desired. Sharing or obtaining microbial strains from other reliable culture collections may be beneficial to expand microbial collections, especially for sensitive or endangered species. However, it is important to consider the possibility of genomic variations in different sublines. Collected and acquired microorganism strains, genetic material (*e.g.*, recombinant plasmids), and associated data should undergo a sufficiently thorough characterization (see *Section D3.5.4. QC for Microorganisms*), including viability (see *Section D3.5.3. QC for Cells, Viability and Vitality*), purity, and authenticity checks as well as confirmation of taxonomy[44].

Protists include a diversity of unicellular (mainly) and multicellular eukaryotes that are not considered animal, plant, or fungi. Protists can be collected from soil[45] and other environments[27], including from their hosts. Natural water sources can be gradually filtered to select protists ranging in size from 3 to 50 microns and the protists individually sorted into wells of a microplate. Flow cytometry and staining can be used to detect phototroph fluorescence and heterotrophs[46]. Macroalgae can be collected by hand or forceps and microalgae can be scraped, brushed or siphoned according to the microhabitat.

### J4.3.7. Plant specimens

Collections of plant genetic resources (see *Section C5. ELSI for Plant Specimens and Data*) are essential for the conservation of genetic diversity to enable sustainable agriculture and response to climate change and for other purposes. Seeds to be preserved need to be collected at near maturity or maturity for optimizing longevity in storage in a repository. They should be removed from the seed's outer surfaces and decontaminated. Water should not be used to preserve the water content of seeds. To maximize the quality, seeds should be processed and transferred to a controlled drying environment within 3-5 days of collection. For fruit seeds, it is recommended to transport the seed within the fruits for protection and avoid dehydration. It is important to provide complete information about the collected seeds, which are crucial in identifying and classifying the specimen. Different practices and techniques for the collection, the preservation, and the regeneration of plant parts are detailed by Panis' group[47]. For herbarium and other plant collections, a multiplicity of plant parts such as roots, foliage, bark, stems, bulbs, flowering structures, *e.g.*, meristem, and pollen,[48] and a range of variation of the plants are generally


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collected. Life cycle stages of the plant as well as the season should be accounted for in collection protocols. Root tips and plant cell cultures can complement a plant collection.

The potential exposure pathways that could result in harm from the plant and its toxins should be recognized and accounted for in the documented collection protocols. Oral ingestion (*e.g.*, hand-to-mouth), cutaneous absorption, and inhalation may occur following touch or exposure with various sections of a plant. A risk assessment should be undertaken and risk management put in place to prevent misidentification, mishandling, and potentially harmful consequences. Appropriate PPE should be provided and used for personnel protection (see *Section F3. Personal Protective Equipment*).

### J4.3.8. Insect Specimens

Different methods can be used to capture an insect; however, the sweep net and aquatic net are the main equipment used to catch specimens. Generally, captured specimens are mounted post-mortem on needles and preserved under specific conditions to avoid premature specimen loss (see *Section G. Facilities* for guidelines on setting up repository conditions). An insect repository can grow rapidly, often with many specimens still in need of being cataloged for the first time, and sufficient space is recommended to support this growth. For the preservation of living insects, specific life cycle stages are often desirable. For insects that undergo hibernation or have a diapause stage, these specimens may be stored at a lowered temperature partially desiccated. Eggs and larvae of certain species can be cryopreserved, some by slow equilibrium cooling, others by vitrification using high CPA concentrations and rapid cooling.

## J5. SPECIMEN PROCESSING

Suboptimal processing can alter different specimen characteristics (*e.g.*, morphological, molecular) and it is advisable for processing procedures to account for the primary preanalytical factors thresholds that may affect fitness for purpose[49], (see *Section D3.6.3. Preanalytical Variation*). Of particular note are the references and resources provided at the end of this section. These include a sizable number of ISO Technical specifications that apply to the preanalytical workflow for in vitro diagnostics, but also have relevance for research. Initially developed within the SPIDIA4P program and CEN/Technical Committee 140, most have progressed to ISO standards and a list of published documents is available[50]. These documents detail specifications relating to handling, processing, and documenting preanalytical factors for specimens such as blood, plasma, urine, and tissue, microbiome DNA, on exosomes from venous whole blood, circulating free DNA (cfDNA) from urine and other body fluids, cfRNA from venous whole blood-plasma, FFPE in-situ staining, and metabolomics from urine, plasma, and serum.

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 F4. Health and Safety Topics*).
- Inspection for accuracy of specimen identifier/label, specimen deficiencies, etc.
- Maintaining specimen integrity (*i.e.*, preserving the structure and usually the function of the specimen, 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 might be a volume/weight less than specified; a major non-conformity for blood specimens might be hemolysis, lipemia (milky), or icterus (jaundiced dark yellow), or a delay in the time-to-centrifugation of greater than one hour (see *Section D3.5.2. QC for Fluid Specimens)*.

If any non-conformity or combination of non-conformities can result in specimen rejection, the rejection criteria should be defined and documented (*e.g.*, specimen identity cannot be determined). Subsequent actions should be described and documented (*e.g.*, specimens that meet the rejection criteria are discarded) (see *Section D3.8.1. Non-Conformities* and more generally *D3.8. Quality Improvement*).

***BEST PRACTICE:*** Non-conformities observed or detected during processing should be identified and documented as should subsequent actions taken.

***BEST PRACTICE:*** When possible, two or more samples per specimen should be processed and stored for redundancy.

## J6. RECEIVING SPECIMENS

Procedures should be in place for receiving specimens and associated data into the repository and specimens that have been collected should be received by the repository according to these procedures. All specimens provided to the repository from outside sources should be confirmed/verified in a Shipment Verification Report maintained by the receiver (see *Section D3.2.2. Storage and Retention of Documented Information*) and a copy provided to the shipper as the site of origin/submitting site (see *Section L. Packaging and Shipping*). Data loggers, where used, should be checked to determine if adverse temperature spikes have occurred. Any problems encountered with a shipment should be communicated to the personnel arranging the shipment (shipper), *e.g.*, issues pertaining to the stability of the cold chain for chilled or cryopreserved specimens. The report should document the following:

- Receipt date and time.
- Shipment tracking number.
- Package and container condition including visible signs of damage, *e.g.*, images.
- Condition of the refrigerant used during shipment.
- Confirmation that:
  - » The number of containers match (if multiples are in the shipment) (see *Section L4. Documenting and Tracking Shipments*).
  - » Specimens received match those listed on the shipment manifest sent with the shipment.
- Discrepancies noted and any resolutions reached.
- The repository personnel recording the entries (name/signature/date).

Specimens should be kept in an environmentally-controlled temporary storage location (also termed quarantine storage) suitable for their storage requirements to prevent degradation while any discrepancies or missing information are being resolved and before being transferred to their permanent storage location. Once received in the repository, the status of the specimens as they move through the system and change location (*e.g.*, temporary storage, permanent storage, processing) should be noted in the appropriate specimen inventory system.

***BEST PRACTICE:*** A quarantine process including the use of designated storage unit(s) should be in place for temporary storage of received specimens where further clarifications or critical information is required.

## J7. RETRIEVAL OF SPECIMENS FROM STORAGE

Retrieval of specimens for shipment or analysis requires strict adherence to protocols for specimen inventory and tracking, as well as adherence to established safety protocols for working with freezers and other storage equipment (see *Section F. Health and Safety*).

### J7.1. Locating Specimens in Storage

The location of specimens to be retrieved should first be verified in the appropriate specimen inventory management system (see *Section I3. Inventory Management System*). A requisition should be generated before specimens are retrieved from storage and retrieval should be performed following the repository's specimen access and use (see *Section K2. Access, Distribution, and Use*), 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.

### J7.2. Specimen Retrieval

Specimens should be located and pulled from storage as documented on specimen requisition forms. If specimens are frozen or cryopreserved, 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 (and adjacent specimens) should be maintained within the acceptable storage temperature range throughout the process. For example, specimens stored in the region of -80 °C can be nested in dry ice throughout the retrieval process to avoid significant temperature differentials from the bottom of the storage container or tube to the top. There are many commercial products available to maintain cold chain temperatures during retrieval, *e.g.*, cryocarts, cryopods, and temperature-monitoring devices developed for


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transport. Specimen handling tools such as cold forceps should be used when withdrawing specimens stored at cold and ultra-low temperatures to prevent warming of the specimens from body contact.

Once retrieved, personnel should confirm that all requisitioned specimens have been included in the pull (see *D3.5. Quality Control Approaches*). 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 K2.2. Review of Access and Use Requests*).

***BEST PRACTICE:*** A quality control check should be performed to ensure that the correct specimens have been retrieved, ensuring the specimens are maintained at temperature.

***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 (see *Section K1. General Introduction for Access, Distribution, Use, Transfer, and Disposal*).

## J7.3. Thawing/Warming and Aliquoting Specimens

### J7.3.1. Liquid and Solid Tissue

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

Large-volume liquid specimens (*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 at room temperature according to a protocol 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 specimen further. A fresh 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 portion from a table-stored frozen specimen without thawing the remainder of the specimen. 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 criteria 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 specimens.

### J7.3.2. Viable Cells

The rate and method of freezing/thawing and cooling/warming specimens can have serious effects on the viability of cells. Specific freezing/thawing, vitrification, and cooling/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 *J3.7. Specimen Preservation* and *J3.8. Freeze/Thaw and Cooling/Warming Cycles*). American Type Culture Collection (ATCC) as a nonprofit, global biological resource center and standards organization develops and updates guides for the culture of different types of cells[51].

Although slow cooling is often best to ensure cell viability of frozen specimens, the opposite process is required when thawing from the frozen state. Specimens should be rapidly thawed for just enough time to thaw visible crystalline ice and so that specimen temperature is still hypothermic (2 – 8 °C). Cells should be quickly diluted in appropriate media to minimize toxicity from the CPA. Dilution protocols (which may include several washing steps in order to gradually dilute and wash out the CPA) should be optimized to circumvent damaging osmotic

effects. In the case of vitrified specimens, optimizing cooling and warming regimens is critical for ensuring the formation and maintenance of a stable glassy state and preventing devitrification and ice nucleation during warming. Therefore, in contrast to controlled-rate freezing protocols, vitrification can involve rapid cooling and rapid warming regimens. For quality control of cells, see *Section D3.5.3. QC for Cells, Viability, and Vitality*.

## J8. SPECIMEN INVENTORY MANAGEMENT

The activities of collection, receipt, and retrieval are inventory related. Inventory management is required as these activities and related processes continuously perturb the inventory. Inventory management of physical specimens can be complex and time consuming. Aspects for consideration include space management, specimen findability, and identification of any weak points in physical specimen inventory, storage, or inventory data.

Repositories should consider implementing some or all of the following practices:

- Initial assessment of appropriate storage format for anticipated duration of storage and periodic assessment of viability of specimens in long-term storage (see *Section D3.5. Quality Control Approaches*).
- Periodic assessment of the fitness of alternative and low-cost storage formats such as fresh (*e.g.*, FFPE, DBS) rather than freezing or cryopreserving[40].
- Periodic auditing of the specimen inventory to ensure the physical inventory matches any documented or online inventory data (see *Section I3. Inventory Management System*). Frequent specimen auditing helps to detect errors and, through corrective action, provide more accurate up-to-date inventory data. Options include auditing of the entire collection or random sampling of different storage units at different times, depending on available resources.
- Monitoring storage space to meet future needs. Forecasting of specimen retrievals against the rate of incoming specimens to calculate storage requirements versus available space. Growth projections should cover the period of time that may be required to acquire new storage space.
- Standardizing storage configuration to reduce overall cost by streamlining maintenance and reducing requirements for spare parts and backup capacity. It can also have positive impacts on emergency management, enabling efficient transfer of specimens in the case of storage unit failure.
- Proactive preventative measures, *e.g.*, maintenance of storage equipment (see *Section H12. Equipment Maintenance, Repair, and Replacement*).
- Optimizing inventory storage space through identification of empty locations (*e.g.*, vacant slots in vial box containers) and either consolidating existing stored specimens or using empty slots for storage of new specimens (also known as defragmentation). This effort can be assisted by an interactive inventory management system (see *Section I3. Inventory Management System*) to identify the empty locations and to update the location of any newly relocated specimens.
- Triage specimens in advance of an emergency or disaster to pre-identify, stratify, and document the criticality of specimen inventory (*e.g.*, with rare or irreplaceable specimens deemed the most critical).
- Create a prioritization strategy to safeguard based on criticality in the event of an emergency, such as depleting supplies of liquid nitrogen for storage.
- Ease of access for rapid retrieval of specimens deemed most critical in the event of an emergency.
- Division of aliquots (or sister specimens) across separate storage units (freezers) to mitigate loss in the event of single point of failure.
- Use of specimen vial containers of the smallest practical size/volume can assist in reduced storage space, energy costs, and costs of shipments, (see *J3.3. Specimen Containers*).
- Selective disposal and or transfer to a new location, where space is limited or no longer available. The repository can review and eliminate selected specimens and/or the data or plan for transfer of specimens to an alternative location (see *Section K4. Transfer and Disposal*).
- Weigh the benefits of automated storage systems against the costs of purchasing, installation, and set-up period and annual servicing and maintenance costs[52-54] (see *Section H4. Automated Storage Systems*).

***BEST PRACTICE:*** A repository should identify strategies that can be used, either separately or together, to help mitigate the risks associated with specimen inventory management.



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# SECTION K: ACCESS, DISTRIBUTION, USE, TRANSFER, AND DISPOSAL

## K1. GENERAL INTRODUCTION FOR ACCESS, DISTRIBUTION, USE, TRANSFER, AND DISPOSAL

A repository should provide for proper and efficient utilization of its collected specimens and associated data. The path to access specimens and associated data should be clear and documented so that stakeholders can understand the process for research use or other intended use of repository contents.

Repositories should establish written policies and procedures addressing how specimens and associated data are accessible, what constitutes appropriate use of the specimens and associated data, and how decisions are made to approve requests for specimens and/or associated data. Such approaches are a key mechanism for both access governance and to avoid underutilization. The repository should also take into account notifications and actions to be taken when retrieval of specimens results in the remaining stock reaching a defined, critical level.

The policies and procedures should take into account that access to repository collections and associated data may be governed by ethical approval, legislation, and regulations, which should be considered prior to release to the end-user especially if monetary benefits arise from their use (see *Section C. Ethical, Legal, and Social Implications*).

Where repositories facilitate access to external parties, the policy for access and use should be transparent and communicated appropriately. Repositories may use communication strategies to promote their services and allow for maximal use of their specimens and associate data (see *Section A5. Communication and Repository Promotion*).

Similarly, policies should be established for specimens and associated data transfer or disposal. Documented procedures for transfer of collections and selective or mass disposal should be in place.

Policies and procedures for access, distribution, use and final destination of the collections should be included in the planning process (see *Section A1.2. Lifespan and Phases of a Repository*) and reflected in the governance of the repository (see *Section A2. Repository Governance*).

All access policies should be developed in compliance with existing regulatory frameworks and approvals, regulations, and applicable laws (see *Section A2.4. Policy Development*).

***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.

## K2. ACCESS, DISTRIBUTION, AND USE

### K2.1. Access, Distribution, and Use Policy and Procedures

Repositories should develop a policy and procedures governing sharing of specimens and data. This should include guidance for determining what constitutes research or other intended use as well as if the specimens and/or data can be externally accessed.

The policies and procedures that guide access, distribution (see *K4. Transfer and Disposal*), and use should consider which specimens and/or associated data are available for sharing and who can access these. How specimens and associated data are made available, including the mechanisms for submission of requests, should be considered. Virtual platforms can be used to facilitate search for repositories that distribute specimens and their associated information, as well as informing potential end-users of existing collection types (see *Section I3.5 Virtual Platforms*).

The review process and criteria for determining whether a request can be filled are also relevant (see *K2.2. Review of Access and Use Requests*), along with a process for appealing decisions. If applicable, an oversight should be provided along with the mechanisms for return of specimens and/or data.

Guidance for prioritization of access (*e.g.*, for access to rare or irreplaceable specimens or for competing requests) and any other relevant criteria should be addressed within the access, distribution, and use policy and procedures[1].

Any exclusion criteria and other restrictions on use should be documented and taken into consideration when reviewing access of specimens and/or data for use. Research exclusions might include genetic research or commercial use and may be specified in associated documentation, and/or other contracts, *e.g.,* Material Transfer Agreements (see *K3. Transfer Agreements*). Requestor exclusion criteria might include previous lack of compliance behavior or for local research use only[1].

#### K2.1.1. Data and ELSI Governance in Access, Use, and Distribution

Data and ethical, legal, and social (ELSI) governance are important in an access, distribution, and use policy for provision of data and should take into account:

- Any standards used to manage and share data (see *Section I3.8. Data Standards*).
- Measures to ensure that specimens are correctly linked to the associated data, where both are provided and, where relevant (*e.g.*, for species other than human), to the specimen voucher (see *Sections J3.1. Identification and Labeling of Specimens* and *L2.1. Shipping Regulatory Requirements*).
- Legal requirements related to specimens and data, protocols and other documents governing the repository, *e.g.*, informed consent (see *Section C2.2. Informed Consent Process*) and intellectual property rights.
- Confidential data including sensitive personal data that needs protection at all times (see Sections *C2.1.1. Privacy and Confidentiality Risk*, and *I2.3.2. Data Privacy*). Data pertaining to humans should have identifying information removed, and where necessary replaced with codes (de-identifying).
- Any contractual agreement(s) such as Material and Data Transfer Agreements (see *K3. Transfer Agreements*). Repositories storing genetic resources obtained from animals, plants, or microbes should be aware of any agreements made with providing countries that outline use 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, including those relating to benefit sharing (see *Section C1.4.1. Benefit Sharing*) should be clarified with the provider and be in line with applicable agreements (such as the Nagoya Protocol, see *Section C1.2. Legal Implications*)[2-5]. See Sections *C3.*, *C4.*, and *C5.* ELSI For Microbial, Animal, and Plant Specimens and Data, respectively).

***BEST PRACTICE:*** Repositories should establish and document policies and procedures governing access, distribution and use, transfer and/or disposal of specimens and associated data, including data-sharing policies. Terms and conditions governing access and use should be tracked by the repository and taken into consideration.

***BEST PRACTICE:*** Repositories personnel should be trained and deemed competent on any policies and procedures related to specimen access, distribution, and use (see *Section E2.1. Training and Competency Program*).

***BEST PRACTICE:*** Repositories should ensure their access, distribution, and use policies and procedures are discoverable and kept up to date, being clearly communicated to external stakeholders, where relevant.

### K2.2. Review of Access and Use Requests

Repositories should establish transparent and efficient processes and procedures for review of specimen and data requests. Requests for specimen and data access and use should undergo some level of scientific and/or administrative review.

Considerations may include:

- Scientific merit and potential impact of the proposed research.
- Whether the research use of both the specimens and data is consistent with previously established priorities, as set by the:
  - Participant/donor (consent).
  - Ethics approval.
  - Repository through agreements appropriate to the nature and purpose of the repository.
- Availability of specimens and data of the specific type requested and usefulness for the intended research method (*e.g.*, of appropriate quality to be acceptable as fit for the intended use).
- Specimen volume/amount requested, with respect to:
  - The total in the repository, and the ability to regenerate or recollect.
  - The proposed use and proposed research methodology.
- Data requested, with respect to specific data elements and any restriction(s) on sharing.
- Adequacy to perform the proposed research in terms of the:
  - Research design, including benefits and risks of the proposed research.
  - Research team, *e.g.*, qualifications and professional reputation.
  - Resources, *e.g.*, research environment and funding.
- Legal and ethical considerations.



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The extent of review and administrative actions may vary depending on the nature of the request and other factors. Examples might include requests for rare specimens needing to be assessed against potential competition for their use; and any additional processing, pre-analysis, or special handling by the repository personnel that might be requested for specimens and/or data. Some repositories may have a cost recovery system for services associated with specimen distribution, as defined in the business plan of the repository (see *Section A3. Repository and Business Planning*). Information about a cost recovery model or service fee should be publicly available and the basis for it should be transparent.

Requests should be reviewed in a timely manner by qualified individuals of an Access Review Panel, including scientific and/or clinical experts on the proposed research and/or different repository stakeholders (see *Section A3.1.1. Specimen Collection and Storage Environment*). The primary custodian should be part of this review panel.

An ethics committee review and approval for the research use of specimens and/or data requested, and documentation of such approval, needs to be obtained preceding the specimen and/or data access request and retrieval (see *Section C1.3. Ethical Review*). This review is especially important if the requested specimen and/or data use falls outside of the previously agreed terms and conditions of use. Consideration of all requests should be documented. Where necessary the appropriate stakeholder(s) should be consulted to clarify the terms and considerations prior to the specimens or data being shared with the requester.

***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 have well-documented and clearly defined criteria for evaluating requests for access consistent with the repository's policies for specimen and data sharing.

### K2.3. Acknowledging Repositories and Reporting Use

In publications resulting from the use of specimens or data, it is appropriate that the repository be acknowledged as the source of the specimens and/or data and/or services, either within the Material and Methods section or in the acknowledgements of the manuscript[4-6]. A recommended format for repository citation has been suggested including a repository ID (such as DOI), name (such as on a material transfer agreement [MTA]), place of residence (including town name), number of accesses, and the date of last access, at a minimum[6].

Repositories may require end-users to provide reports on the use of specimens and/or data provided and include this requirement in the associated transfer agreement (see *K3. Transfer Agreements*). Repositories may ask end-users to provide the repository with data derived from individual specimens or aggregate research results, such as those that are relevant for the health of participants, according to local regulations. End-users may share specimen-associated data under the terms of the initial MTA or under a new agreement to improve the overall research value[3],4.

Repositories may specify a date by which specimen end-users should provide data, taking into consideration any special requirements that some end-users may have to delay dissemination of results as specified in study protocols or to secure intellectual property rights. Repositories should have mechanisms in place to enable follow up when the deadline for the return of data has been reached (see *K2.1. Access, Distribution, and Use Policy and Procedures*).

***BEST PRACTICE:*** Repositories supporting research should establish policies and procedures for repository acknowledgement, *e.g.*, in publications, and for reporting requirements about the use of specimens and data provided by the repository. These requirements should be specified within the transfer agreements.

## K3. TRANSFER AGREEMENTS

A Material Transfer Agreement (MTA) is a contract that governs the transfer of research materials between two organizations, often termed a provider and a recipient. Transfer agreements are necessary to regulate the transfer of specimens and/or data. Such agreements can be known by a variety of titles that might be particular to domains or to the organization concerned. A non-exhaustive list of commonly used titles of transfer agreements are provided here:

- Material Transfer Agreement (MTA).
- Biological Transfer Agreement (BMTA).
- Data Transfer Agreement (DTA).
- Material and Data Transfer Agreement (MDTA).

Other types of transfer agreements without the title of Material Transfer Agreement (MTA) may be used to generally serve the same purpose and include the similar components to those detailed within an MTA. MTA guidelines are provided by the World Health Organization.

The transfer of data may be handled either alongside the transfer of specimens or as a separate agreement. This agreement may constitute a stand-alone Data Transfer Agreement (DTA) or the necessary terms may be included in a Material and Data Transfer Agreement (MDTA). Where an MTA is used for specimen and data transfer, the repository should ensure that any data being transferred are adequately addressed within the relevant term(s). For the purpose of this document, all of these agreements will be referred to as MTAs.

An MTA documents the obligations and responsibilities of parties involved in the transfer of materials and additionally serves as a mechanism for ensuring traceability. Such a contract is used for the following situations:

- The transfer/relocation of collections from one organization to another, *e.g.*, for custodianship.
- Distribution of defined specimens and/or data to an end-user for a defined research purpose in line with repository policies on access and distribution, and data sharing.

Specific terms are used and defined within such agreements, such as the use of "materials" and/or "specimens" (*e.g.*, whole animals, plants, microorganisms, human tissue or parts thereof, reagents, cell lines, plasmids, and vectors). The MTA defines the rights of the provider and the recipient with respect to the materials and any derivatives. An MTA should document the permissible use or uses for the collection/specimens and data being transferred.

The repository should account for any restrictions for the sharing of data that may be specified in the terms and conditions of the MTA. Such restrictions might be related to the non-collation of data previously provided to the end-user for other unrelated and approved use or restrictions on sharing of data with third parties who will provide an analytical service using the specimens for the receiving party.

### K3.1. Contents of Transfer Agreements

Repositories should develop and execute a signed agreement with recipients or end-users prior to transfer of specimens and/or data by using a template previously provided or revised by their organization's legal expertise. Similarly, an agreement should be in place when the repository is the recipient. Agreements governing the transfer of specimens and/or associated data to a recipient should address the following elements for transfer agreements at a minimum:

**Purpose of the transfer, including:**

- Description of the specimens and/or data to be transferred (further documentation may be provided as annexes where necessary).
- The intended use.

**Use of the specimens/data:**

- Ownership and rights relating to the specimens and data.
- Clear statements about sharing of benefits (see *Section C1.4.1. Benefit Sharing*).
- Restrictions on the use of the specimens/data (*e.g.*, specimens/data may not be banked, sold, used in other projects, for commercial or therapeutic activities, redistributed to third parties; restrictions included in the informed consent or prior informed consent).
- Intellectual property rights.
- Publication/authorship rights and acknowledgement of the contributions of both parties.
- Provision of feedback to the provider.
    - » Publications, reports, raw data, and/or incidental findings about specimen use and/results.
    - » A reasonable timeframe to evaluate and review any planned publication, new patent applications, etc.
- Final destination (*e.g.*, return or attested disposal) of surplus specimen or data upon research completion or agreement termination.

**Biosafety:**

- Sign-off by recipients to handle all specimens with the necessary safety methods and a statement that the provider is not liable for any health risk or damage that may result from the recipient's unsafe handling of the specimens.
- Requirements for appropriate biosafety knowledge for handling.


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**Data protection:**

- Custodianship, access, and control of transferred data.
- Protection of data against unauthorized access.
- Restrictions on re-identification of participants (particularly where de-identified specimens are provided).
- Requirements for maintaining traceability, protection of donor/participant privacy and confidentiality, and for shipping and storage conditions.

**Additional terms:**

- Terms of agreement, dispute resolutions, identification, payment schedule, and rights and title to the research performed.
- Termination of the agreement, amendment, and partial invalidity.
- Other factors that may govern the transfer (*e.g.*, definitions, insurance, warranties, contractual requirements, such as non-disclosure agreements (NDA), local regulations, or other considerations).
- The mechanisms for enforcing authorized use and remediating inappropriate or unauthorized use.

***BEST PRACTICE:*** A contractual agreement such as an MTA or similar should be executed to document the obligations and responsibilities of parties involved in the transfer of materials/data to and from a repository prior to shipment. The agreement should be in place before the transfer occurs and documentation for such transactions should be retained.

***BEST PRACTICE:*** Repositories should have templates of this document that can be used or modified as needed. The specific circumstances of the particular arrangement should be considered and the template tailored as appropriate.

## K4. TRANSFER AND DISPOSAL

### K4.1. General

Within a repository, specimen and data life cycle activities may include disposal (selective or wholesale) and transfer. A number of ethical, legal and social implications are associated with these activities, necessitating careful consideration of all relevant stakeholders, agreements, and regulations (see *Section C. Ethical, Legal, and Social Implications*). Collections or specimens with associated data may be transferred from the repository or disposed of for a number of possible reasons. These might include:

- Approved access and distribution for a defined purpose according to the Access, Use, and Distribution Policy.
- When specimens have fulfilled their original purpose, retention time (see *Section A1.1. Types of Repositories*), or are no longer suitable for their intended purpose.
- In response to an emergency or disaster event (see *Section B2.2. Business Continuity Plan*).
- Relocation of unused specimens to another custodian (see *Section G10. Relocation of a Repository*).
- Associated data deemed critical are incomplete, lost, or unknown, *e.g.*, the legal basis for storage has been lost, the identity of the specimen(s) is not known.
- Unacceptable biorisk (see *Section F4.1. Biorisk Management*).
- Repository closure due to political, strategic, or other decisions (see *Section A1.2. Lifespan and Phases of a Repository*).
- When required by ethical obligations (*e.g.*, withdrawal of consent), study design, or regulations (see *Section C. Ethical, Legal, and Social Implications*).
- Specimens have not been accessed or used or custodianship cannot be verified.

Costs for retrieval, disposal, and/or transfer of specimens or collections should be considered and included in the repository budget plans (see *Section A3.2. Business Planning and Sustainability*).

### K4.2. Specimen and Data Transfer

Transfer of specimens and data can be determined and pre-arranged (*e.g.*, for collaborations or acquisitions for use, as a loan, or relocation), or can be part of emergency response planning (see *Section B2.2. Business Continuity Plan*). The process can apply to just a few specimens and/or data variables or to the entire collection.

#### K4.2.1. Specimen Transfer

While distribution and shipping of cryogenic specimens or even sets of specimens is a routine practice, larger transfers or complete relocations can present some significant challenges. Different strategies may be used

depending on the number of units being transferred. Prior to transfer, transient warming tolerance thresholds for the specimens should be evaluated (see *Section L. Packaging and Shipping*). Handling of specimens during specimen retrieval (see *Section J7. Retrieval of Specimens from Storage*) and transfer has the potential to affect the specimen integrity (see *Section J3. Specimen Integrity*) and may affect the quality of resulting data obtained from these specimens (see *Section J3.8. Freeze/Thaw and Cooling/Warming Cycles* and *D3.5. Quality Control Approaches*). Risk assessment should be undertaken for cooling/warming, freeze/thaw, and vitrification/devitrification cycles occurring when cold-stored specimens are transferred.

In situations that require transfer of an entire collection or relocation of a repository, careful planning should address maintenance of cold chain during transport, organization, and accession of specimens at the destination and transfer of data (see *Section G10. Relocation of a Repository* and *J6. Receiving Specimens*).

#### K4.2.2. Data Transfer

Data to be transferred should be backed up before migration to protect against loss or corruption of the transferred data. The repository should continue to ensure confidentiality and security of the specimens and data during transfer (see *Sections C2.1. Managing Research Risks for Participants*, and *I2.3. Data Security and Privacy*). When a Shipping Manifest is used, sufficient data should be included to permit identification of the physical specimen collection (see *Section L4.1. Shipping Manifest*). Approved requests for access should be assessed to determine what data fields will be transferred if not all.

Repositories may wish to predetermine what data elements may be approved for specific or common purposes, so that data distribution is in line with consent/authorization. Where anonymization is a criterion for the purpose of exporting data for distribution, then only non-personal data elements should be added to a data file for transport. The process for this preparation should be verified as not containing any personal data prior to data transfer.

Electronic data migration can be facilitated either in a single event or can be completed in phases (*e.g.*, for blinded or masked analyzes, the repository may wish to address the timing of sending of certain data variables with the requestors). Full transfer of the data in a single event is completed within a limited window of time. An active live inventory management system (IMS) is likely to experience downtime while the data go through processing and transition to the new system. For migration over different phases, both the old system and the new can run in parallel, which eliminates downtime or operational interruptions during implementation.

Data management mechanisms must be in place in order to manage the transfer (see *Section I3.7. Interoperability, Portability, and Reconciliation*). Management of specimen location data and tracking of specimen movements can be performed using an IMS or similar collections management system. These can include end-to-end barcoded chain-of-custody tracking.

The physical specimen inventory should be aligned to any documented or online inventory data (see *Section J8. Specimen Inventory Management*) as soon as feasible after relocation.

***BEST PRACTICE:*** Data management mechanisms and data security controls should be in place during data transfer.

### K4.3. Specimen and Data Disposal

Disposal of specimens and data may have ethical and/or legal considerations. Depending upon the nature of the study population and the repository, repositories and end-users may be required to dispose of unused specimens according to local, legal, ethical, and *safety* rules, or traditional or religious customs for the disposal of human remains. Alternatively, end-users may be requested to return unused specimens to the repository (see *Section C. Ethical, legal and Social implications*).

***BEST PRACTICE:*** Repositories should document the final destination of specimens, data, or collections through disposal or transfer to a new custodian and retain the documents in the archival records of the repository.

#### K4.3.1. Specimen Disposal

Safety precautions appropriate for the type of specimens and risk level need to be observed when specimens are disposed (see *Section F4. Health and Safety Topics*). The repository should have documented procedures to address disposal of all the specimen types stored in the repository. Repositories should document specimen disposal including the reason for disposal. This information can provide important indicators for areas needing improvement either in specimen handling or repository operations and risk management.



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#### K4.3.2. Data Disposal

Disposal of data should be irreversible with no chance of recovery and in a manner that leaves no possibility for reconstruction of information and should be conducted in accordance with the repository data management procedures (see *Section I2. Data Management*). Paper records can be incinerated, shredded and cross shredded, pulped, or pulverized. Digital data may be destroyed by deleting or overwriting information, reformatting, pulverizing, magnetic degaussing (exposure to a strong magnetic field), or destroying any physical media (*e.g.*, CD-ROMS, DVDs). Extra care should be taken with sensitive or confidential information, particularly when an external destruction service is used (see *Section A4.3. Contracted Services and Consultants*). Disposal should be clearly documented.

Data destined for disposal could be placed on lockdown, *i.e.*, cannot be used or shared, until disposal is approved according to the justification provided, and disposal can be performed by authorized personnel.

***BEST PRACTICE:*** Repositories should develop policies for disposal of specimens, data, and collections, including the criteria for continued retention or final destination and approvals needed.

***BEST PRACTICE:*** Repositories should have documented procedures in place for regularly scheduled reviews of the inventory to ensure that specimens and data meet criteria for continued retention.

***BEST PRACTICE:*** A repository should monitor specimen and/or data disposal due to compromised quality as part of quality management for the repository.

### K4.4. Legacy Planning

Legacy planning involves the preparation for a large-scale operational change or closure of the repository[7]. This should be considered separate from and in addition to planned collection transfers as part of risk management (see *Section B. Risk, Emergency, and Disaster Management*). Enactment of a legacy plan may be as a result of the natural termination of a collection due to completion of the project or research purpose for which it was compiled, an operational change such as change in repository or project leadership, and/or a loss of funding, for example. The legacy plan should include procedures for the assessment of the current state of the collection and a framework for deciding on the retention/disposal or transfer of collections.

***BEST PRACTICE:*** Establish a legacy plan for the repository in the event of a significant operational change or repository closure; see *Section A3.1.2. Services to be Provided*.

***BEST PRACTICE:*** Complete assessments of legacy collections and determine continued retention/transfer/disposal in line with access and use policies.

### K4.5. Inherited Collection

The repository should conduct a collection assessment to review any inherited or legacy collections and reconcile with any associated data and provenance documentation. The available provenance documentation data (*e.g.*, consent forms and other contractual agreements) review should inform if future use is possible. An assessment of specimens and other data quality should additionally be undertaken to determine fitness for purpose (see *Sections C2.2.2. Types of Consent*, *D1. General Introduction to Quality Management*, and *I3.2. Specimen Descriptors*).

A lack of provenance information can severely impact the potential utility of an existing collection. For biodiversity collections, collection permits, Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) permits, or a Nagoya protocol compliant material transfer agreement (when specimens are subject to the Nagoya protocol [see *Section C1.4.1. Benefit Sharing*]) should be available to accompany the transfer. If unavailable, due diligence will need to be completed and documented to ascertain the specimen's origins and if appropriate re-negotiate or repatriate the specimens/collection.

The repository should also assess the research value against current repository strategy aims and policies (see *K2.1. Access, Distribution, and Use Policy and Procedures*). Based on the collections' assessment, a decision should be made to address collection needs (subject to available resourcing) to digitize (see *Section D3.5.7. QC for Digital Imaging*) and disseminate, dispose, or transfer the collection.

## K4.6. Transfer to New Custodian

A repository may encounter a situation where some or all of its collections can no longer be supported within the existing framework. A decision may need to be made regarding the continuance of the collections. This eventuality should already be described in the business plan (see *Section A3.2. Business Planning and Sustainability*). Repositories should develop plans at the time of establishment or as soon as possible thereafter for the final destination of specimens and/or data should the repository be terminated for any reason. The final destination, 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 *K.4. Transfer and Disposal*).

The final decision to transfer, dispose of, or partially dispose of a collection may be based on an assessment of the existing permissions for the collection (consent, regulatory compliance, etc.), utility for future uses (research value), potential new custodians/repositories, and costs associated with each possibility.

When a decision is made to transfer the collection or to transfer oversight for the collection to a new designee outside the repository, the Director (*i.e.*, repository leadership) is responsible for the preparation and effective transfer. The critical stakeholders should be informed of the impending change and approve the request to transfer or other (reducing the collection and / or disposal) before conducting the transfer.

Transfer agreements (see *K3. Transfer Agreements*) should be established and any existing terms of ownership/use from original collection acquisition which may need to be renegotiated with the country/institution/party of origin should be highlighted (see *K4.2. Specimen and Data Transfer*).

***BEST PRACTICE:*** For collection transfer to a new custodian, assess the potential for research use interest and establish transfer agreements with the receiving organization.

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# SECTION L: PACKAGING AND SHIPPING

## L1. GENERAL INTRODUCTION TO PACKING AND SHIPPING

Many repositories routinely send specimens to different entities, either within their own region or to varying destinations around the world[1]. For some, this may include relocation of part or all of an entire collection (see *Section G10. Relocation of a Repository*) or the transfer of specimens and data for distribution (see *Section K4.2. Specimen and Data Transfer*). Courier and shipping logistics companies generally refer to personnel arranging a shipment as the *shipper*, and the personnel receiving a shipment as the *consignee*. Shipping can pose significant risk to specimen integrity; particularly where cold temperatures are required. Risks should be carefully considered and managed appropriately (see *Section B. Risk, Emergency and Disaster Management*).

## L2. 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.

### L2.1. Shipping Regulatory Requirements

Packaging and shipping should conform to applicable regulations and legislation. For example, air shipments should conform to International Air Transport Association (IATA)[2] and ground shipments should conform to applicable national, regional, or federal standards. The personnel arranging the shipment (shipper) should first determine how to classify 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. Any components applied to the specimens (*e.g.*, preservatives, excipients) should also be considered. Substances with a designated UN number (United Nations hazardous materials four-digit identifiers) on the corresponding (Material) Safety Data Sheet may be considered dangerous goods. National or federal transport regulations as well as those from the International Civil Aviation Organization (ICAO)[3] and IATA should be consulted in order to properly classify the specimens to be included in a shipment.

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 (Convention on International Trade in Endangered Species of Wild Fauna and Flora)[4] permit and additional paperwork may be required for field collection of organisms that are endangered or protected or pose a hazard to human or animal health. CITES documentation should 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. International shipments of disease agents of humans and animals or of vectors may require additional permits (see *Section C. Ethical, Legal, and Social Implications*).

Many countries require that personnel involved in the transport of dangerous goods receive training and be deemed competent in the packaging, labeling, documentation, and shipment of dangerous materials before undertaking shipping (see *Section E. Training and Competency*). As regulations change, training may need to be updated (see *Section C1.2.1. Compliance*). Furthermore, personnel preparing shipments should be trained to understand the conditions (*e.g.*, temperature, humidity) required for shipping different types of specimens.

### L2.2. Shipping Conditions

#### L2.2.1. Shipping Temperature

To preserve specimen quality, shipment temperature should be monitored (when required for fitness for purpose and where feasible) and documented, and the possibility for fluctuations in temperature should be minimized, through packaging design and the selection of appropriate courier expertise. The following are typical temperature conditions required for transport of specimens and the insulation/refrigerant helpful to maintain that temperature:

- Ambient (passive) and controlled ambient (15 °C to 30 °C): Insulated packaging that may include vacuum panels and phase change materials (PCM) to buffer and protect against extreme heat or cold ambient conditions.
- Refrigerated (2 °C to 8 °C): Wet ice or gel packs (conditioned at –15 °C, designed for refrigerated temperatures, or PCM 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. Dry ice (solid carbon dioxide) is considered a hazardous material and appropriate labeling should be included. IATA packing instruction 904 (IATA PI 904) requires that dry ice use be clearly indicated by a diamond-shaped, black-and-white label with the UN 1845 designation. Arrangements must be in place to facilitate adequate ventilation so that pressure build-up does not rupture the packaging.
- Frozen (at or below –150 °C): Liquid nitrogen vapor phase (LNVP) dry shipper, also referred to as a dry vapor shipper, shipping Dewar, or cryoshipper. Dry vapor shippers are insulated containers that contain non-pressurized refrigerated liquid nitrogen ($LN_2$) 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 (see *Section H2.1.2. Large Storage Vessels*).

When used, a courier's ability to replenish refrigerant in the event of a delay should be assessed. Dry ice/$LN_2$ level checking and replenishment by the courier (logistics provider) while en route should be requested when shipping internationally, for delays encountered, or when transit is expected to last several days.

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

### L2.2.2. Shipping Humidity

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

### L2.2.3. Shipping Data loggers

Specimens being shipped from one site to another are often packed with a data logger that can record physical attributes of the shipment while in transit. Single use or reusable temperature data loggers (*e.g.*, thermocouple probes, radio-frequency identification [RFID] tags, color-coded vaccine labels) can be used to determine and/or record the internal package temperature during transit. The resulting temperature recording informs the receiver of any possible temperature excursions that the payload may have encountered (see *Section J6. Receiving Specimens*). More sophisticated data loggers may be used to record additional data, such as impacts, vibrations, tilt, humidity, light, and geolocation of a shipment, based on the time or route in transit and the need to monitor these factors. For information on data logger validation, see *L5.2. Cold Chain Validation*.

## L2.3. 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 *L5. Cold Chain*). Timing of the delivery of shipments should be considered as well[1]. Shipments should be pre-arranged in agreement with the recipient and scheduled so that they do not arrive on a holiday or weekend. Attention should be paid to weather forecasts and extreme environmental or political occurrences (*e.g.*, volcano eruptions, earthquakes, regional or local unrest) that might affect transport routes to ensure the shipment is not delayed.

## L2.4. Packaging Shipments

The quantity of specimens to be transported impacts 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


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the right size for the number of specimens and amount of refrigerant 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.

***BEST PRACTICE:*** To minimize risk of loss, splitting duplicate specimens between shipping units and shipping in separate shipments should be considered.

#### L2.4.1. Packaging Considerations

- Specimens should be surrounded on all sides by the refrigerants used rather than being placed either on top of or underneath the refrigerant.
- If dry ice blocks or sheets are used as refrigerant, the specimen containers and contents should be protected from piercing by any sharp edges created through the sublimation of dry ice during transit.
- After the specimens and the refrigerant have been placed into the container, empty space should be filled with absorbent substances, 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.
- Waybills (*e.g.*, air waybills, sea waybills; see *L3.3. International Shipments*) should not be reused.

## L3. VALIDATION AND VERIFICATION OF SHIPPING CONDITIONS

### L3.1. Review of Packaging Test Report

The personnel arranging the shipment are responsible for choosing appropriate packaging for the material being shipped. Initial validation of the packaging should be undertaken to ensure that the packaging regulations and transport requirements are met. A packaging SOP should state what conditions each packing material is suited for and detail how to prepare the shipment. Test reports should be reviewed for each new lot of packaging material received from the supplier.

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, impact).

### L3.2. Test Shipments

In some situations, especially relating to extremely valuable or rare specimens, repositories may choose to first send a test shipment that approximates the characteristics of the actual shipment. This may inform the personnel arranging the shipment as to the adequacy of packing coolants and also serve to identify any potential obstacles for the successful shipment, including possible customs inspection delays. When conducting a test shipment, a temperature-recording device or an irreversible temperature indicator can be added to the container to help determine that temperature requirements were fulfilled.

***BEST PRACTICE:*** Shipping conditions (see *L2.2. Shipping Conditions*) should be validated prior to conducting an actual shipment.

***BEST PRACTICE:*** Shipping SOP deviations such as temperature excursions during test shipments should be investigated and the shipment conditions optimized where possible. The repository may wish to perform the test shipment again under the optimized conditions.

### L3.3. International Shipments

In addition to complying with regulations and legislation (see *L2.1. Shipping Regulatory Requirements*), international shipments may require:

- Customs invoice (or pro forma invoice) declares the contents, quantities, weights, harmonized system code(s), and values of the contents in the shipment to customs authorities for clearance purposes. Shipper (who arranges the shipment) and receiver (consignee) details are included. Use of the organization's letterhead for such an invoice is recommended (or sometimes required). The services of a customs broker can be helpful or even critical for customs clearance. Certain couriers and third-party logistics providers can provide this service, considerably simplifying the process. Requests for expedited customs clearance can be made of the courier, where required.

- The (air) waybill that acts as a contract/receipt of shipment, designed for (air) cargo and is generally provided by the courier company for completion by the shipper.
- Any permit(s) and/or sanitary certificate(s) required (may be necessary for the recipient to provide).

The documentation required and the methods of preparation may differ depending on the regional jurisdictions involved for the shipment and any courier parties involved. All shipping documentation should accompany the shipment container(s) as per the courier instructions and relevant regulations. Where displayed externally, an extra copy of the documentation should be placed inside the container in case of the externally displayed documents going missing along the way.

***BEST PRACTICE:*** When acting as a shipper, a repository should prepare all documentation required for an international shipment in conjunction with the recipient and ensure that the necessary documentation accompanies (each stage of) the shipment. When acting as a recipient, documentation required for import should be provided to the shipper.

## L4. DOCUMENTING AND TRACKING SHIPMENTS

The shipping of specimens from one physical site to another is a regulated, multi-step process that should be documented to ensure proper tracking and delivery. Prior to sending specimens, a Material Transfer Agreement (MTA) or similar should be in place between the party organizing the shipment (shipper) and the receiving party (see *Section K3. Transfer Agreements*). Both parties have responsibilities in the shipping process. The shipper should create a manifest to record the contents of the shipment, and a shipment log that fully documents the transport and allows for tracking of the shipment en route through to delivery receipt. The recipient is responsible for providing verification that the shipment was received intact and in good order, and that the contents match the entries in the manifest. Each repository should maintain a record of the shipment logs and manifests. Personnel arranging the shipment should take sufficient care to check all is in place prior to initiation of the shipment (see *L3.3. International Shipments*) and that records are retained thereafter (see *L4. Documenting and Tracking Shipments*). Both the personnel arranging the shipment and the recipient should track all packages while in transit.

### L4.1. Shipping Manifest

The personnel arranging the shipment should create a manifest list of the specimens included in the shipment. This list is usually assigned a number (Manifest ID) for tracking purposes within the IMS and throughout the shipping process. The manifest should contain the specimen IDs and key data attributes of the specimens, to facilitate their identification and use at the destination site. Having these key data elements associated with the specimens best supports interoperability, and fitness-for-purpose (FFP). The manifest should be included in the shipment and should also be sent electronically to the recipient at the time of transport initiation.

The list of data elements in the manifest may include:

- Manifest ID (may be linked to the reference number for the request for access (see *Section K2. Access, Distribution and Use*).
- Repository name and address.
- Study/project name.
- Organism type.
- Specimen IDs (see *Section J3.1. Identification and Labeling of Specimens*).
- Specimen type(s), numbers of aliquots/replicates of each type and mass or volume.
- Recommended storage criteria (*e.g.*, temperature range).

Other data variables that can be added to the manifest or can be provided to the recipient separately (see *K4.2.2. Data Transfer*) include:

- Body site of specimen location detail, as applicable.
- Fixation/stabilization.
- Additive/preservative.
- Cell type and viability, as applicable.
- Extraction or processing method.
- Specimen attributes (*e.g.*, tissue character, format, stain).
- Vial/container type.
- Quality attributes pertaining to FFP *e.g.*, certificate of analysis/report (see *Section D3.5. QC Approaches*), such as assays performed, and results, *e.g.*, hemolysis state, concentration and quantification method, freeze/thaw cycle.



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Where relevant and applicable, the units should be provided. Any specimen associated data provided should be linked or definitely associated with the specimen to which it specifies.

### L4.2. Notification of Shipment

The personnel arranging the shipment should notify the recipient that a shipment is scheduled to arrive on a specific date or dates. The recipient should confirm that they are able to receive the package and have the required facilities and capacity for reception and storage before the personnel arranging the shipment establish a pick-up day and time with the courier and release the shipment to the courier. The personnel arranging the shipment should provide a 24-hour emergency contact for all packages, particularly those transporting infectious agents and other dangerous goods.

***BEST PRACTICE:*** Advance notification of shipment, tracking information and manifest should be communicated electronically from the originating site (shipper) to the receiving site (consignee), along with a request for acknowledgment of notification from the receiving site. A paper manifest should always accompany the shipment.

### L4.3. Shipping Log and Tracking

The shipper arranges transport of the shipment, usually with a logistics provider that has experience with biological materials. The shipment tracking ID is generally synonymous with the waybill number and is generated by the logistics provider. This tracking ID should be provided to the recipient as soon as it is available. A shipping log (often electronic) is used to record and track key shipping details. These details may include:

- Logistics provider/courier company name and contact information.
- Shipment tracking ID composed of a string of characters or a barcode from the logistics provider can be found on the (air) waybill.
- Customs documents, import/export permits (*e.g.*, CITES), and approvals.
- Safety precautions conforming to the package labels (*e.g.*, IATA regulations, safety data sheets, UN designation), emergency contact information.
- Contact information:
    - Shipment origin source (shipper) name, address, and contact details for personnel arranging shipment.
    - Shipment destination (receiver or consignee) name, address, and contact details for personnel receiving shipment.
- Date (and time) of shipment pickup.
- Number of containers within the shipment (aligned with the customs invoice, manifest, and packing slip).
- A packing slip, internal to the shipment and separate from the manifest, providing a succinct summary of the specimens and their numbers being shipped.
- A Shipping Verification Report form to be completed by the consignee upon arrival of the shipment at the destination (see *L4.5. Shipment Receiving and Verification*).
- Shipping temperature (*e.g.*, ambient temperature, dry ice, liquid nitrogen vapor phase dry shipper; see *L2.2.1. Shipping Temperature*).
- Data logger ID number(s) and location(s) within the payload (where applicable).
- Digital pictures of boxes/containers, where practicable.

### L4.5. Shipment Receiving and Verification

Confirmation of receipt and the condition upon arrival should be documented using a Shipping Verification Report Form for every delivery or shipment of specimens. This form could originate from the shipper or the recipient. If originating from the shipper, it should be sent with the shipment/delivery. It should be completed and returned/sent to the shipper and any discrepancy between the shipment as sent and as received should be resolved (see *Section J7. Receiving Specimens*).

Upon receipt at destination, the minimum information to be captured on the Shipping Verification Report Form should include:

- Date received.
- Name of receiver.
- Name of person(s) unpacking/checking the shipment (if provided).
- The report/output of the any data logger(s).

- Any deviations from specified procedure, *e.g.*, discrepancies between the shipping manifest and the contents of the shipment.
- Condition of the shipping container(s), in particular to highlight any issues with shipment including indications that a specimen has been compromised. This may include image(s) of any damage.

Additional records of any temperature deviations from the data logger(s) or any damage to the shipping container(s) should be added to the specimen records in the IMS and as part of the Shipment Verification Report form.

## L5. COLD CHAIN

### L5.1. General

The cold chain is the temperature-controlled supply chain (below ambient), which must remain unbroken over all steps of collection, storage, and distribution events (*e.g.*, from field, to repository, to end users). The purpose of the cold chain is to safeguard perishable and regulated specimens and preserve specimen quality and integrity. Cold chain temperatures range from a typical 2-8 °C for specimens requiring refrigeration to below -150 °C for cryopreserved specimens.

The cold chain distribution process is an extension of the Good Manufacturing Practice (GMP) applied to all drugs and biological products and required by various health authorities and regulatory bodies. The same cold chain principles apply to non-GMP human, animal, plant, fungal microbial, and other specimens. All distribution and storage processes should be validated to ensure that there is no negative impact on the quality of the specimens (see *Section D3.6 Validation, Verification and Qualification*).

***BEST PRACTICE:*** The management and record keeping of a cold chain should include all measurements, qualifications, validation, and shipping documentation. All equipment and SOPs for cold chain operations should perform reliably.

### L5.2. Cold Chain Validation

Cold chains should be validated in advance and controlled throughout the life cycle of the specimens. Cold chains incorporate the following:

- Logistics providers: Specialist couriers, carriers, and logistics providers with technical ability to link with airlines for real-time status, generate web-based export documentation, and provide electronic tracking. Repositories should consider using providers that additionally offer on-the-ground troubleshooting, where practicable.
- Transport and shipping containers: A wide variety of refrigerated vehicles, warehouses, insulated shipping containers, and other specialized packaging exist. These containers/packages should be tested and evaluated as fit for purpose and comply with appropriate shipping regulations for packaging class and dangerous goods transportation (*e.g.*, flammable preservatives, corrosives, dry ice, ICAO, IATA, road, rail, or maritime regulations), where relevant.
- Tracking: Data loggers (see *L2.2.3. Shipping Data loggers*) and/or other devices (*e.g.*, thermocouple probes, RFID tags, color-coded vaccine labels) monitor and record temperature or other conditions during all steps at and between one location and the next (*e.g.*, field to repository, between laboratories or from repository to clinical trial sites).
- Documentation: Standard operating procedures (SOPs) should underpin chain of custody and proper records (see *Section D3.3. Standard Operating Procedures*).

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ISBER Head Office: 1618 Station Street, Vancouver, BC, V6A 1B6, Canada
Contact Information: T: +1.604.484.5693 • F: +1.604.874.4378 • E: *bestpractices@isber.org* • *www.isber.org*

# Appendix A: References and Internet Resources

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ISBER Head Office: 1618 Station Street, Vancouver, BC, V6A 1B6, Canada
Contact Information: T: +1.604.484.5693 • F: +1.604.874.4378 • E: *bestpractices@isber.org* • *www.isber.org*

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## INTERNET RESOURCES

The internet resources are provided for additional information or as resources to supplement the content within the Best Practices. Because of the everchanging nature of the internet, the links and resources provided here were live and up to date at the time of the Fifth Edition publication. As these are external resources that are not managed by ISBER, we cannot assure that these links will remain active or updated.

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ISBER Head Office: 1618 Station Street, Vancouver, BC, V6A 1B6, Canada
Contact Information: T: +1.604.484.5693 • F: +1.604.874.4378 • E: *bestpractices@isber.org* • *www.isber.org*

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# Appendix B: Terminology

Generally, the terms defined below are in the context of this document. In some cases, the terms are used differently in different fields or contexts.

ACCESS AND BENEFIT SHARING – The fair and equitable sharing of both monetary and non-monetary advantages or gains arising from the use of specimens and associated data in line with relevant agreements, policies, laws, etc.

ACCREDITATION – Third-party attestation conveying formal demonstration of competence, impartiality, and consistent operation in performing specific activities.

ACQUISITION – Specimen and/or data collection that is not directly conducted by repository personnel. Specimens and/or associated data may be obtained, received, or sourced by a repository from parties external to the repository, *e.g.*, other repositories, commercial sources, transfer of legacy collections.

ALIQUOTS – Subdivided portions of a specimen that are stored individually. Note that aliquots may not always be homogenous, *e.g.*, tissue specimen aliquots such as sections or slides.

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.

ANONYMIZATION – Process of removing all identifying information from specimens and data. In most cases, the possibility of re-identifying or re-contacting the participants/donors is negligible.

ANONYMOUS – A specimen or associated data where identifiable personal information was not collected or, if collected, was not maintained or cannot be retrieved. An anonymous specimen or associated data may be a result of anonymization.

APPLICATION PROGRAMMING INTERFACE (API) – Software that allows two or more computer programs or systems to communicate with each other using requests and responses.

ASSENT – Agreement by participants who are under the legal age for informed consent. Note that assent may be followed by re-consent once the legal age has been reached.

ASSOCIATED DATA (*i.e.*, data associated with specimens) – A broad and inclusive term that includes any information directly or indirectly related to or linked to the specimen. Information may include but isn't limited to specimen ID, collection details, volume/amount, preservative/fixative methods, exposure data, treatment data, as well as indirectly linked information, *e.g.*, analytical data, images, or feedback/assessment from end-users.

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

AUTOPSY – Postmortem examination of the organs and tissues of a body to determine or confirm the cause of death or pathological conditions. Referred to as necropsy in relation to animals.

BIOBANK – See REPOSITORY.

BIOBANKING – Performing functions associated with a repository. See REPOSITORY.

BIOLOGICAL MATERIAL – See SPECIMEN.

BIOLOGICAL SAFETY CABINET (Biosafety cabinet, biosafety hood) – Cabinet designed to protect the user against biohazards and the specimens from contamination. Differs from a fume hood in that fume hoods are not designed to protect specimens from contamination.

BIOHAZARD – A risk to human health or the environment arising from a biological substance.

BIORISK –The severity and likelihood of an adverse impact resulting from a specific biohazard. The adverse impact can be the consequence of unintentional exposure, accidental release, loss, theft, misuse, diversion, unauthorized access, or intentional release.

Source: Partially adapted from ISO/DIS 35001 Biorisk management for laboratories and other related organisations, 3.17 Note 1 to entry *https://www.iso.org/obp/ui/#iso:std:iso:35001:dis:ed-1:v1:en.*

BIOSAFETY – Strategic and integrated approaches and practices (*e.g.*, physical, facility, and procedural controls) to manage, including eliminating, minimizing, and mitigating relevant biorisks.

BIOSECURITY – The practices and controls that reduce the risk related to the loss, theft, or misappropriation of biological substances (*e.g.*, pathogens, viruses).

BUSINESS CONTINUITY – Ensuring critical operations proceed during a disruption and recover after the disruption including safeguarding core assets, the interests of stakeholders, and repository reputation.

CALIBRATION – The process of comparing the output or indication on a device (*e.g.*, measurement instrument) with a value traceable to an applied standard (often a national or manufacturer standard), within a specified accuracy.

CERTIFICATION – Issue of a written statement (certificate), based on a decision of an independent body that fulfillment of specified requirements for a product, service, person, or system has been demonstrated.

CHAIN OF CUSTODY – Refers to the chronological paper or electronic documentation trail showing the full process of consent (where applicable), acquisition, transfer, handling, and disposition of specimens and associated data.

CHILD SPECIMEN – Aliquots or derivatives of a parent specimen. Note that this does not refer to familial relationships.

CODED – A specimen or associated data that has had personal identifying information removed such that the participant is no longer identifiable. A unique code or coding system is used to retain a link between specimens, participants and data for the purpose of authorized re-identification. The code is highly restricted and not available to end users. See - PSEUDONYMIZATION.



ISBER Head Office: 1618 Station Street, Vancouver, BC, V6A 1B6, Canada
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COLD CHAIN – Managing the temperature of thermally sensitive specimens in order to maintain quality and safety from the point of origin through all activities to the end-user

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 – This term is used in two ways throughout the document. 1. Verb: The activity of obtaining specimens and/or associated data. 2. Noun: Refers to a set of specimens and/or data that has been collated primarily for research purposes.

CONFLICT OF INTEREST – A real, potential, or perceived situation in which an individual's interests could result in personal, professional, or organizational benefit or compromise their judgment, decisions, or actions in a professional capacity.

CONFORMITY ASSESSMENT – The demonstration that specified requirements (conformities) are fulfilled. The process can have negative outcomes, *i.e.* demonstrating that the specified requirements are not fulfilled (non-conformities).

Source: Adapted from ISO/IEC 17000:2004 Earth-moving machinery - Conformity assessment and certification process, Terms and definitions 3.1 *https://www.iso.org/obp/ui/#iso:std:iso:tr:19948:ed-1:v1:en:term:3.1*.

CRYOPROTECTANT – An additive or mixture of additives that allow living cells, tissues, organs, and organisms to survive exposure to cryogenic temperatures

CUSTODIANSHIP – The caretaking responsibility in regard to the management and governance of specimens and data within a repository or a collection.

DEHYDRATION – Removal of water from a tissue.

DERIVATIVE – A child specimen which is of a different specimen type from that of the parent specimen, *e.g.*, plasma is a derivative from blood

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.

DISPOSAL – Process of permanently and wholly eliminating a specimen, collection, or stored data beyond repair or re-instatement. May also be referred to as destruction or culling.

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.

DONOR – a) A living or deceased human or animal that is the source of specimens and/or associated data, b) a person, organization, or government submitting biodiversity or environmental specimen(s) and/or data. c) This term may also refer to a financial donor supporting the repository.

END-USER – An individual who receives and uses specimens and/or data or partakes in services offered by the repository.

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.

ERGONOMICS – An applied science that explores an individual's interactions with their work environment and develops systems and/or employs tools, products, and practices that facilitate improvement of work conditions for optimal safety, efficiency, and comfort.

ETHICS COMMITTEE – Any board, committee, or other group formally designated by an institution, regional, or governmental authority or independently accredited to:

- Undertake an independent ethical review of research involving humans, human specimens and/or data.
- Approve or deny the initiation of research.
- Periodically review ethically approved research.
- May also be called an Institutional Review Board, Ethics Review Board, Research Review Board, Independent Ethics Committee, etc.

EXPLICIT CONSENT – Documented written or verbal agreement by an individual to contribute specimens and/or associated data for use in research. May also be referred to as "express" or "direct" consent.

FEDERATED COLLECTIONS – Created when specimens and/or data are collected, processed, and stored at physically separate sites that each function as the specimen custodian for its local collection while related data is managed through a central database.

FIT FOR PURPOSE; FIT FOR INTENDED PURPOSE – The specimens and/or associated data meet the criteria associated with the use and are deemed applicable and appropriate for that intended use by the end-user. It represents an exacting specification of quality.

FREEZE-DRIED – Dehydrated for storage by conversion of the water content of a frozen specimen to a gaseous state under vacuum. Also called lyophilized.

GENOMICS RESOURCES – In a biodiversity context, any genetic material of actual, potential, or perceived value

Source: Adapted from The Convention on Biological Diversity Article 2. Use of Terms *https://www.cbd.int/convention/articles/?a=cbd-02*.

GLASS TRANSITION (TG) – 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 specimens to deteriorate.

ICE NUCLEATION - Ice nucleation is an event that occurs during the cooling of a specimen and is the point at which the first ice crystals are initiated; often applied in the context of cryopreservation such as controlled rate cooling. See SEEDING

IDENTIFIER/IDENTIFYING/IDENTIFIABLE INFORMATION – Data (*e.g.*, name, national identification number, medical record, or pathology accession number) that may enable the connection of the data to the individual.

IMPARTIALITY – A principle of decision-making based on established objective criteria, rather than on the basis of bias, prejudice, or benefitting one over another for improper reasons (for example in the event of a conflict of interest).

Source: Institute and Faculty of Actuaries Section 5: Principle 3 - Impartiality *https://actuaries.org.uk/standards/standards-and-guidance/the-actuaries-code/the-actuaries-code-principle-3-impartiality/section-5-principle-3-impartiality/*.

INCIDENT – Any unplanned occurrence that deviates from standard operating procedures or applicable government laws and regulations during specimen retrieval, processing, labeling, storage, or distribution that may affect subsequent use of those specimens.

INFORMED CONSENT PROCESS – A process during which information is proactively communicated to an individual that may lead to voluntary (and reversible) agreement or permission to provide specimens and/or associated data for use in research. The process involves two-way communication between the repository personnel and the individual. The decision to participate is physically or electronically documented (*i.e.*, explicit) often in an informed consent form. For biodiversity contexts, see Prior Informed Consent.

KEY PERFORMANCE INDICATOR – Quantifiable measure used to evaluate a repository's progress towards an intended result.

LABEL – Any written, printed, or graphic material on or affixed to a specimen container or package.

LIFE CYCLE – The life cycle of a specimen and associated data includes all of the handling activities such as collection/acquisition, storage, distribution, return of research results, and disposal. It may include externally provided processes under the control or management of a repository. It is acknowledged that activities after distribution are generally not under the control of the repository.

LIFESPAN – The duration of time encompassed by the phases of a repository from its conception to termination. Phases can include initiating, planning, executing, monitoring, and terminating.

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 OR DRY VAPOR SHIPPER – A dry or vapor shipper is a double wall evacuated and super-insulated Dewar vessel with solid adsorbent placed around the specimen space. Sacrificial cryogen (liquid nitrogen) is introduced, absorbed, and held by the adsorbent such that there is no free liquid. Temperature is maintained at liquid nitrogen vapor level until the liquid nitrogen evaporates from the absorbent material. The absence of free liquid allows for shipment of the product with a non-hazardous classification by air, sea, or road.

LOT – Quantifiable measure used to evaluate a repository's progress towards an intended result.

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.

MUTUALLY AGREED TERMS (MAT) – In the context of Access and Benefit Sharing for biodiversity, a contract between user and provider of genetic resources that regulates benefit-sharing, third-party use, etc.

OPTIMAL CUTTING TEMPERATURE (OCT) COMPOUND – Fast freezing, specimen-embedding matrix often used to maintain tissue integrity and stability at freezing temperatures for applications such as histopathology, molecular biology, or long-term storage.

PARENT SPECIMEN – The specimen from which aliquots or derivatives (child specimens) originate. Note that this does not refer to familial relationships.

PARTICIPANT – A person who is the source of the specimen and/or associated data. This individual is involved in the process of providing the specimen and/or associated data through voluntary participation based on informed consent or waiver of consent.

POSTHUMOUS BIOBANKING AUTHORIZATION – Permission provided by the participant prior to death, by next of kin and/or by a legally authorized representative to collect or use specimens and/or associated data from deceased participants, for example during autopsy or for organ donation.

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.

PRIOR INFORMED CONSENT (PIC) – In the context of Access and Benefit Sharing for biodiversity, the permission provided by the competent authority of a providing country and/or indigenous peoples and local communities before biodiversity genetic resources are accessed.

PROCESSING – Any procedure employed after specimen collection but prior to its distribution, including preparation, testing, and releasing the specimen to inventory and labeling.

PROFICIENCY TESTING – An external quality assessment to examine repository processes and personnel performance.

PROSPECTIVE – A study or collection maintained for expected or likely use in the future.

PSEUDONYMIZED - A specimen or associated data that has had personal identifying information removed such that the participant is no longer identifiable. Use of a unique code, encryption, etc., can be used to retain a link between specimens, participants, and data for the purpose of authorized re-identification. The code, encryption key, etc., is highly restricted and not available to end users. See PSEUDONYMIZATION.

PSEUDONYMIZATION - The process of removing personal identifying information from data such that the participant is no longer identifiable. Different techniques such as use of a unique code, reversible encryption, etc., may be used to retain a link between specimens, participants, and data for the purpose of authorized re-identification. The code, encryption key, etc., is highly restricted and not available to end users.

QUALITY ASSURANCE – A broad approach for aiming to prevent issues within processes that could impact on the fitness for purpose of specimens and data. Part of quality management.

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

QUALITY MANAGMENT – Any component or activity that impacts on the quality of a specimen and its associated data

QUALITY MANAGEMENT SYSTEM – Integrates policies and practices for the full spectrum of quality in a repository. Can be facilitated manually, *e.g.*, with paper-based documentation, supplemented by electronic systems, or be entirely based on a software solution, according to the resources available to the repository.

RECONCILIATION – Process of data validation where data errors are identified and rectified using defined procedures and actions.



ISBER Head Office: 1618 Station Street, Vancouver, BC, V6A 1B6, Canada
Contact Information: T: +1.604.484.5693 • F: +1.604.874.4378 • E: *bestpractices@isber.org* • *www.isber.org*

REPOSITORY – In its simplest form, a place where collected parts or the whole of organisms and/or environmental specimens are stored for safekeeping. In the context of this document, the term applies more extensively to any entity focused on management and operations of specimens and associated data *primarily* intended for research purposes. Alternative terms may include biobank, biorepository, biological resource center, collection (*e.g.* microbial collection center, data collection center), cryogenic biobank, digital repository, gene bank, biodiversity biobank seed bank, virtual biobank, veterinary biobank, culture collection, gene bank, environmental specimen bank, tissue bank, cell bank among many others.

RETENTION TIME – Duration a specimen, data, or document is within the jurisdiction of the repository.

RETRIEVAL – Accessing specimens or data for use, transfer, processing, distribution, and/or disposal.

RETROSPECTIVE – Relating to or being a study or collection (as of a disease) that looks back on or deals with past events or situations.

RISK – An isolated or continuing situation that may lead to danger, harm, loss, or a negative outcome. May negatively impact individuals, organizations, finances, facilities, the environment, etc. See also BIORISK for risks associated with biological agents.

SAMPLE – See SPECIMEN.

SEEDING – Seeding is a process applied to a solution cooled below its melting point in order to generate an ice nucleation event (*e.g.*, touching the solution with an ice crystal). See ICE NUCLEATION.

SHIPPING MANIFEST – A written description of the contents of the shipped package.

SPECIMEN – In this document, a specimen is a specific biological or environmental material (*e.g.*, tissue, fluid, leaf, soil, or other) either provided by or from a single participant, donor, organism, population, (ecological) community, or environmental location. Often used interchangeably with the terms biological material, biospecimen, or sample within a repository.

Note that the use of the word specimen in this document differs from how it is most often used in biodiversity/environmental contexts, where "specimen" describes an individual organism (animal, plant, etc.) used as a representative of its species or population and the tissue, cells, DNA etc. obtained from the specimen is generally termed a "sample."

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.

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.

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.

VALIDATION – Confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled.

Source: ISO9000:2015 Quality management systems - Fundamentals and vocabulary Section 3.8.13
*https://www.iso.org/obp/ui/#iso:std:iso:9000:ed-4:v1:en*.

VERIFICATION – Confirmation, through the provision of objective evidence, that specified requirements have been fulfilled. Note the activities carried out for verification are sometimes called a qualification process.

Source: ISO9000:2015 Quality management systems - Fundamentals and vocabulary Section 3.8.12
*https://www.iso.org/obp/ui/#iso:std:iso:9000:ed-4:v1:en*.

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.

VOUCHER SPECIMEN – In biodiversity contexts, denotes preserved organisms in whole or part (or other physical evidence or images) on which observations and critical analyses have been performed and that are accessible for reference and validation purposes and to underpin future research.

VULNERABLE PARTICIPANT/GROUP – An individual or group who may require additional special consideration or protection in the context of research, due to a potential for inequitable treatment, exclusion, coercion, or increased risk of individual or group harms. "Vulnerability" may occur as a consequence of the nature of the research and/or circumstances of the individual or group and may be either temporary or permanent.

WARM ISCHEMIA – The amount of time that an organ, tissue, or specimen 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 - 1 dimensional

2D - 2 dimensional

2FA - Two-factor Authentication

3Rs - Replacement, Reduction, and Refinement

ABS - Access and Benefit Sharing

AI - Artificial intelligence

ALCOA+ - Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring, Available

AMN - Mercosur Association for Standardization

API - Application Programming Interface

ASCII – American Standard Code for Information Interchange

ASCP BOC - American Society for Clinical Pathology's Board of Certification

ATCC - American Type Culture Collection

AWERB - Animal Welfare and Ethical Review Body

BAT - Biobank Assessment tool

BAP - Biorepository Accreditation Program

BBNJ - Biodiversity Beyond National Jurisdiction

BIMS - Biobank Inventory Management System

BLOB - Binary Large Objects

BMTA - Biological Transfer Agreement

BRC - Biological Resource Centers

BRISQ - Biospecimen reporting for improved study quality

CABRI - Common Access to Biological Resources and Information

CAP - College of American Pathologists

CAPA - Corrective/preventive actions

CBD - Convention on Biological Diversity

CDC - Center for Disease Control

CEN - European Committee for Standardization

cfDNA - Circulating free DNA

cfRNA - Circulating free RNA

CIOMS - Council for International Organizations of Medical Sciences

CITES - Convention on International Trade in Endangered Species of Wild Fauna and Flora

COI - Conflicts of interest

COPANT - Pan American Commission for Technical Standards

CPA - Cryoprotectant additives

CPD - Continuous professional development

CSP - Cloud services providers

CSV – Comma-Separated Values

CTRNet - Canadian Tissue Repository Network

CVL - Cervical vaginal lavages

DBS - Dried Blood Spot

DIN - DNA Integrity Number

DNA - Deoxyribonucleic acid

DMP - Data management plan

DMS - Data management system

DMSO - Dimethyl sulfoxide

DTA - Data Transfer agreement

DwC - Darwin Core

EBRCN - European Biological Resource Centre Network

eDNA - Environmental DNA

EDTA - Ethylene diamine tetraacetic acid

ELSI - Ethical, Legal, and Social Implications

EMbaRC - European Consortium of Microbial Resources Centres (EMbaRC)

ENCR - European Network of Cancer Registries

ENSCONET - European Native Seed Conservation Network

EQA - External quality assurance

eRNA - Environmental RNA

ESB - Environmental specimen banks

EU - European Union

FAIR - Findable, Accessible, Interoperable, and Reusable

FAO - Food and Agriculture Organization

FFP - Fit for purpose

FFPE - Formalin-fixed paraffin-embedded

GCP - Good Clinical Practice

GDP - Good Distribution Practice

GDPR - General Data Protection Regulation

GGBN - Global Genome Biodiversity Network

GLP - Good Laboratory Practice

GMP - Good Manufacturing Practice

GPS - Global Positioning System

GUI - Graphic User Interface

GxP - Good Practices

H&E - Hematoxylin and eosin

H&S - Health and Safety

HEPA - High-efficiency particulate absorbing

HIC – High-income countries

HIPAA - Health Insurance Portability and Accountability Act

HVAC - Heating, Ventilation, and Air Conditioning

IACUC - Institutional Animal Care and Use Committee

IARC - International Agency for Research on Cancer

IATA - International Air Transport Association

ICAO - International Civil Aviation Organization

ICD-9-CM - International Classification of Diseases Ninth Revision, Clinical Modification

ICD-10 - International Classification of Diseases Tenth Revision

ICD-O - International Classification of Diseases for Oncology

ICO - Informed Consent Ontology

IEC - Independent ethics committee

IMS - Inventory management system

IRB - Institutional review board

IUNC - International Union for Conservation of Nature and Natural Resources

IQ - Installation Qualification

ISO - International Organization for Standardization

IT - Information technology

JIST - Japanese Industrial Standards Committee



ISBER Head Office: 1618 Station Street, Vancouver, BC, V6A 1B6, Canada
Contact Information: T: +1.604.484.5693 • F: +1.604.874.4378 • E: *bestpractices@isber.org* • *www.isber.org*

KPI - Key performance indicators
LED – Light-Emitting Diodes
LIMS - Laboratory Inventory Management System
LNVP - Liquid nitrogen vapor phase
LMIC - Low/low-middle income countries
$LN_2$ - Liquid nitrogen
LPSN - List of Prokaryotic names with Standing in Nomenclature
MALDI-TOF - Matrix-assisted laser desorption/ionization-time of flight
MAT - Mutually agreed terms
MedDRA - Medical Dictionary for Regulatory Activities
MDTA - Material and data transfer agreement
MFA - Multi-factor authentication
MIABIS - Minimum Information About Biobank data Sharing
MINE - Microbial Information Network Europe
MIRRI - Microbial Resource Research Infrastructure
MSDS - Material safety data sheets
MTA - Material transfer agreement
NDA - Non disclosure agreement
NIST - National Institute of Standards and Technology
OBIB - Ontology for BioBanking
OCT - Optimal cutting temperature compound
OECD - Organization for Economic Cooperation and Development
OQ - Operational Qualification
PCM - Phase change materials
PCR - Polymerase chain reaction
PIC - Prior informed consent
PNU - Prokaryotic nomenclature up-to-date
PPE - Personal protective equipment
PQ - Performance qualification
PT - Proficiency testing
QA - Quality assurance
QBRS - Qualification in Repository Science
QC - Quality control
QM - Quality management
QMS - Quality management system
QR - Quick response
RBC - Red blood cells
RFID - Radio-frequency identification
RIN - RNA integrity number
RNA - Ribonucleic acids
RT - Room temperature
SDS - Safety data sheets
SMART - Specific, Measurable, Achievable, Relevant, Time-bound
SME - Subject matter expert
SNP - Single nucleotide polymorphism
SNOMED – Systematized Nomenclature of Medicine Clinical Terms
SOP - Standard operating procedures
SPREC - Standard PREanalytical Code
STR - Short tandem repeats
SWOT - Strengths, weaknesses, opportunities, and threats
TC - Technical Committee
TEER - Transepithelial electrical resistance
TOR - Terms of reference
TRUST - TRansparent User-friendly System of Transfer
TUNEL - Terminal deoxynucleotidyl transferase dUTP nick end labeling
UPS - Uninterrupted Power Supply
UV - Ultraviolet
VeNom - Veterinary Nomenclature
WHO - World Health Organization
WMA - World Medical Association
WYSIWYG - What you see is what you get
XLS - Excel Binary File Format
XML – Extensible Markup Language

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# BEST PRACTICES: RECOMMENDATIONS FOR REPOSITORIES

## FIFTH EDITION

**ISBER Head Office**
750 West Pender Street – Suite 301
Vancouver BC V6C 2T7, Canada
Contact Information:
T: +1.604.484.5693
F: +1.604.874.4378
E: *bestpractices@isber.org*
*www.isber.org*