# NIDDK Central Repository Specimen Archival Guidance

*Practical guide to building specimen collections for study protocols and future research use in compliance with NIDDK and NIDDK-CR policies*

# Contents

# Introduction

## Scope

This document provides general and specific information for NIDDK-funded clinical cooperative agreements or consortia, and establishes practices and procedures for creating and submitting specimen collections to the Biorepository component of the NIDDK Central Repository (NIDDK-CR) Program for future research use in accordance with the NIH Data Management and Sharing Policy and the NIDDK Central Repository Resource Archival and Sharing Policy (NOT-DK-24-003).

This guidance is designed to assist NIDDK-funded clinical cooperative agreements or consortia, "study groups," in building suitable and representative specimen archival sets that meet submission requirements and are suitable for future secondary use by the broader research community. A "representative archival set" is defined as a set of specimens that includes a portion of every material type collected at every timepoint, from every consented participant.

Each section includes information on best practices that can facilitate the planning and collection activities necessary to acquire, preserve, and set aside specimens for sharing for secondary research that are fit for the purpose intended and maximize future scientific utility. We encourage study groups to regularly refer to this document throughout the planning and active study protocol phases to ensure that the processes used for specimen acquisition and preservation are appropriate and effective. Study groups can also reach out to the NIDDK-CR Biorepository for guidance or suggestions.

## Background

NIDDK is interested in ensuring the sharing of research resources developed through NIDDK-funded networks and consortia for secondary research as a fundamental component to fulfilling NIDDK's mission. In accordance with NIDDK policy, NIDDK-funded multicenter clinical studies are expected to set aside and plan to share a representative specimen archival set. NIDDK-CR was established to support the receipt, storage, and distribution of such specimens. Study groups that are eligible and are required or intend to submit specimens to NIDDK-CR must adhere to NIDDK-CR policies and procedures.

Before specimens can be submitted to NIDDK-CR, each study protocol must be approved for deposit. The process includes review and approval of the NIDDK-CR Resource Archival and Sharing Request proposal to onboard a study (an "archival plan"), and the Informed Consent document language relevant to storage and future use of data and specimens. The process requires close collaboration between NIDDK Program staff, Study staff, and NIDDK-CR staff through the entire lifecycle.

## Best Practices for Setting Up Specimen Collections

When building a specimen collection for eventual transfer to the Biorepository component of NIDDK-CR, study staff should consider the project goals, the types of specimens needed to meet those goals, necessary materials/supplies for processing and storage, including temporary and long-term storage, labeling, and specimen metadata. They should also consider the potential future uses, by study investigators and secondary use by the broader scientific community, ensuring that specimens are properly consented for analyses that are unforeseen at the time of study enrollment or have not been invented yet. Additionally, they should be aware that these details need to be recorded at the individual and/or vial level, as they will ultimately influence the overall quality of the collection and its potential value to the larger community. Furthermore, careful planning of the budget, staffing, facilities and equipment, and quality control and specimen inventory software needs are key while setting up a specimen collection.

**Budget Planning** is essential for building, maintaining, and transferring a high-quality specimen collection to the NIDDK-CR's Biorepository component. Study groups planning or required to submit specimens must consider how they will budget for the necessary infrastructure to support the collection, processing, and temporary storage employed through the project's lifecycle. For example, the study groups will need to account for labor costs for experienced staff during the active study phases to collect and process the specimens, as well as after the study concludes for support activities such as specimen retrieval, packaging, and shipment to the NIDDK-CR Biorepository facility. In addition, study groups need to budget for administrative costs, laboratory consumables, and specimen processing. Specimen collections that are accepted for deposit and meet submission criteria can be transferred to the NIDDK-CR Biorepository at no additional cost to the study group. That is, the Biorepository component will cover shipping costs, including providing shipping labels and necessary materials, for transferring specimens from a centralized location to NIDDK-CR. The NIDDK-CR Biorepository may also supply collection kits for the archival set if it is demonstrated to be a cost-effective use of NIDDK-CR resources. For this, study groups must submit comparative pricing estimates showing the costs they will incur for the collection kits.

It is important to note that the NIDDK-CR Biorepository does not function as the primary centralized location to store specimens intended for internal or ancillary use during the active phase of the study. Therefore, study groups also need to budget for having a centralized facility outside of NIDDK-CR Biorepository to store specimens during the active phase of the project and to transfer specimens to the NIDDK-CR Biorepository at regular intervals or at the end of the study protocol. Legacy studies, which have historically received primary centralized support from NIDDK-CR Biorepository during the project's active phases, are expected to identify and use an outside facility at their next competitive renewal.

Study groups are encouraged to discuss repository-related budget planning with their designated NIDDK Program staff. Before a grant is awarded, NIDDK-CR cannot advise individual study groups on budget planning beyond publicly available information to prevent the appearance of giving a competitive advantage. Once the grant is awarded, NIDDK-CR will work with study groups to develop cost-effective plans for designing, maintaining, and transferring a high-quality specimen archival set.

**Staffing Expertise** extends beyond clinical, statistical, and assay skills to support the study protocol's execution. Study groups must consider having personnel onboard with the necessary skills and expertise to help design, build, and maintain a specimen collection, with a clear understanding of repository best practices.[1] These individuals will be crucial in developing proper documentation and an operations manual for specimen and specimen attribute data collection, processing, preservation, and inventory control, as well as ensuring compliance with the packaging and transport of biological substances, and should have the appropriate credentials to perform such tasks. Additionally, these individuals will play a key role in selecting a representative specimen archival set that meets NIDDK-CR submission requirements per NIDDK-CR policy and as described herein. NIDDK-CR recommends that staff with the necessary expertise remain available through the end of the funding period to coordinate and manage transfer logistics of the specimen archival set, including generating electronic manifests, resolving discrepancies, and answering questions during specimen accessioning and curation.

**Facilities and Equipment** must be appropriately sized to collect, process, store, and maintain the entire specimen collection throughout the entire project lifecycle. When selecting the external, centralized facility to store specimens during the active phase of the project, study groups should consider whether the facility (and the equipment) meets recommended best practices. For example, current best practice[1] recommends that specimen storage facilities be operated with effective temperature controls, good air circulation, good lighting, and adequate security, with backup emergency power. Ideally, these facilities will have systems in place to allow for local and remote equipment temperature monitoring. It is also recommended that these facilities have emergency plans in place to address equipment failures, power outages, and other hazards (floods, fires, earthquakes). Ideally, to ensure consistent cold-chain management, they will provide round-the-clock temperature monitoring methods, along with routine equipment maintenance and documentation of repairs. Equipment, such as mechanical freezers, should be fitted with stainless steel racks designed to optimize storage space.

Study groups should consider facilities' capacity and capabilities to store specimens according to their ideal storage temperature, including room temperature, refrigerated, and ultralow temperature units, such as vapor phase Liquid Nitrogen (LN2) at -180°C or mechanical freezers at -80°C. They should ensure selected facilities have adequate dedicated and backup equipment throughout the entire project lifecycle and facilitate efficient transfer of specimens for primary analyses and for the eventual transfer of the archival set to NIDDK-CR. NIDDK-CR strongly recommends transferring specimens to the Biorepository component at regular intervals to protect against catastrophic loss.

**Quality Control** (QC) measures must be implemented to ensure the quality and consistency of specimens collected throughout the project's lifecycle, as well as the accuracy of their attribute data. In alignment with best practices, study groups should establish systems and procedures to maintain specimen quality and ensure staff adherence to the same by developing an effective QC plan. Common QC measures include periodic reconciliation of specimen attribute and inventory data, regular cross-checks of inventory data against physical specimen locations, integrated

[1] Guidelines for Human Biospecimen Storage, Tracking, Sharing, and Disposal within the NIH Intramural Research Program, 2019. ISBER Best Practices: Recommendations for Repositories (5th Edition, 2023).

quantification, purification, and other quality assessment checks, along with the use of standardized values and formats for specimen types and related specimen attributes to maintain consistency during the active phase of the project and maintain a high-quality specimen collection. NIDDK-CR requires that the study coordinating center and its centralized laboratory/biobank staff implement a process to electronically track the specimen inventory and monitor specimens from the point of collection through their deposition in NIDDK-CR Biorepository (e.g., Laboratory Information Management System (LIMS) software). In addition, NIDDK-CR has specific quality control requirements, including the use of electronic manifests, provision of specific specimen attribute metadata, and the use of controlled vocabulary or standardized term details, which are provided in other sections that follow.

## Guidelines for Setting Up Specimen Collections

### A. Designing a Representative Specimen Archival Set

According to NIDDK and NIDDK-CR policy, selected study groups (multicenter clinical studies funded through cooperative agreements) are required to proactively plan for the creation of a representative archival set of specimens specifically designated for potential secondary use in future research. Designing a specimen collection and setting aside a set for future research use requires deliberate planning and expertise. This planning should occur at the protocol level and prior to specimen collection (i.e., before participant enrollment). Decisions should include those regarding specimen types to be collected, volumes, aliquoting schemes, vial type selection, and labeling practices among other things. Below, we provide detailed guidance on aspects study groups should consider when designing a collection for eventual archival into NIDDK-CR.

1. **Specimen (Material) Types:** The collection should include representative specimen vials for each material type planned to be collected from all consented participants, along with comprehensive metadata and biological attributes to ensure specimens are suitable for future research applications and can contribute meaningfully to scientific advancement. NIDDK-CR recognizes that for certain study protocols, it may not be practical to include all planned material types in the archival set. Similarly, the NIDDK-CR Biorepository might not be able to accept all material types planned for collection; for example, the Biorepository generally only accepts human-derived biological specimens that do not require further processing. However, there are cases where unprocessed specimens, non-human specimens, or other materials can be proposed for submission and accepted, such as whole blood, environmental samples, or other types of material directly related to human specimens already proposed for submission as part of the archival collection.
    - NIDDK-CR Biorepository classifies material types into six major categories: Biological Macromolecules, Fluids, Solids, Cells, Environmental, and Swab (Cellular/Solid). NIDDK-CR requires that study groups utilize a standardized Specimen Material Types vocabulary for their submissions. **Table A** provides examples of the standardized vocabulary for each material type that may be accepted as part of an archival set and the required accompanying specimen attributes that must be included in the specimen labels, electronic manifest, or other approved specimen metadata dataset.

2. **Volumes and Aliquoting Schemes:** Study groups should propose an archival set, justifying the proposed volumes and quantities in terms of anticipated future utility. NIDDK-CR recommends that study groups plan for the inclusion of "pristine" single-use aliquots in their archival plans as well as larger volume (stock) vials, balancing the number of vials and volume to be submitted with short-term and long-term storage costs. Pristine vials are defined as never-thawed specimens. These single-use vials should be created at the point of initial specimen processing to preserve the integrity of the specimens and minimize the need for freeze-thaw cycles. Study groups should also consider the increased cost and effort needed to aliquot a previously frozen specimen before processing specimens for temporary storage or assaying.
    - NIDDK-CR does not impose minimum or maximum volume or aliquot thresholds for the archival set; it only requires that the set is representative of the overall study population. Although NIDDK-CR does not impose minimum/maximum thresholds, study groups should consider the impact of archiving too low/too high volumes or quantities. Volumes below 1.0 to 1.5 mL per participant, per time point, and per sample type may add unnecessary burden to future research use by artificially increasing the threshold for release. Excessively high volumes or aliquot vials may be cost-prohibitive for both short- and long-term storage.
    - Study groups should design a volume and an aliquoting scheme for each material type that will be collected. A common archival set typically includes 20% to 30% of the total study specimen collection and ideally includes 100% of the enrolled participants, and no less than 90% to 95% of the enrollees. It should also include at least three to five single-use aliquots and one to five larger volume vials per participant, per time point, and per sample type. Once a proposed archival set has been approved, study groups are encouraged to submit the specimens at regular intervals during the active study period, based on participant and specimen accrual rates, rather than at the end of the study. **Table B** provides examples of an aliquoting scheme that may be accepted as part of an archival set, recognizing that different material types, volume yields collected, and aliquot schemes can vary widely.
    - **Best Practice:** Study groups should propose an archival set volume and an aliquoting scheme in terms of anticipated future utility for the research community, considering that NIDDK-CR Biorepository does not normally accept screening timepoints unless there is a compelling justification to include them. Also, specimen vials associated with baseline timepoints are generally in significant demand, and study groups should consider archiving more vials associated with baseline timepoints than from ongoing study visits. It is also important to note that NIDDK-CR cannot guarantee acceptance of excess vials or those that exceed the original archival plan proposal for a given material type/visit/participant. NIDDK-CR will consider accepting excess specimens based on the scientific value of the collection and other factors.
3. **Vial Selection:** In an effort to standardize the vial types in the NIDDK-CR Biorepository, and to support automation, NIDDK-CR strongly encourages the use of self-standing vials that are sterile, RNase, DNase, and pyrogen-free with external threads and with silicone O-rings that assure a leakproof seal. NIDDK-CR can provide cryovials that are returned to the Biorepository, provided this is a cost-effective use of NIDDK resources. If the study group will be selecting their own vials for the archival set, these must be selected based on the material and volumes that will be

stored and are specifically designed and tested to withstand ultra-cold units such as -80°C freezers and liquid nitrogen freezers (-180°C), and when applicable, the analytical goals of the study protocol. Study groups designing a specimen collection earmarked for deposit into NIDDK-CR Biorepository should also consider short- and long-term storage, standardization across enrolling sites, applicability of existing and potential future automation, as well as NIDDK-CR restrictions or requirements.

- NIDDK-CR Biorepository generally does not accept glass tubes or tubes containing materials that require further processing, as these cannot always be distributed. Study groups must deposit specimens using vials suitable for the material and volumes being stored, and designed for the recommended long-term storage temperatures.
- It is important to understand that not all specimen containers are suitable for every application or storage condition. Also, cryovial caps or other closure systems can greatly affect specimen integrity if they break or leak, and they can also impact costs related to purchasing, storage, and transportation. NIDDK-CR Biorepository recommends storing 0.2 mL of material in a 0.5 mL tube rather than a 2.0 mL tube. The vial diameter of these tubes can vary slightly, but should be in the 12.5-13.2 mm range. It is also recommended that tubes be externally threaded to avoid overfilling. **Table C** provides examples of different vial types and common volumes and temperature ranges.
- **Best Practice:** Study groups designing a specimen collection and archival set for deposit into NIDDK-CR should consider that automated laboratory techniques are becoming more prevalent. NIDDK-CR Biorepository recommends that, when possible, specimens be collected in vials that conform to the high-density SBS rack configurations recommended by the Society for Laboratory Automation and Screening (SLAS) standards[2] and support a wide range of storage conditions. These vials should also feature two-dimensional (2D) barcodes on the bottom. These characteristics make them ideally suited for automated workflows using liquid handling, enable automated barcode reading and capping, and ensure compatibility with automated sample management systems. Study groups should avoid specimen vials with attached loop caps, strip-type tubes, and non-self-standing (conical) vials. 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 the leachability of products into the specimens, evaporation, and degradation under handling and storage conditions. Container and cap composition should also be resistant to the chemical nature of the specimens and/or media and compatible with any preservatives used. It is important to note that liquid nitrogen (LN2) 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 LN2 is trapped inside the specimen vial or container. Therefore, it is critical that the storage vessels selected are rated for the appropriate temperature ranges and that staff wear appropriate personal protective equipment when handling these materials.

[2] The Society of Biomolecular Screening (SBS) now SLAS, together with the American National Standards Institute (ANSI) defined a standard for microtiterplates in 2004. The first proposal for the implementation of this standard was released in 1995.

4. **Vial Labeling:** NIDDK-CR defines vial labeling as referring to both the physical label placed on the specimen vial or container ("label stock") and the text and barcode information printed on that label ("label information"). NIDDK-CR requires that study groups that are required or intending to submit specimens to NIDDK-CR Biorepository develop a labeling plan for uniquely identifying each specimen vial. Specimen vials must retain a link to the study participant's research data being submitted, and must be free of direct personally identifiable information (PII) and protected health information (PHI).
    - When developing vial labeling plans, study groups should ensure each specimen has a unique identifier at the aliquot level (i.e., multiple aliquots of the same specimen cannot share the same exact identifier, but must have at least an additional aliquot number that differentiates each aliquot vial from its sister aliquots). Failure to include this in labeling plans will require additional resources to inventory, retrieve, and distribute, which may result in specimen rejection or require specimen relabeling before these can be accepted. On rare occasions, NIDDK-CR may cover the costs of relabeling, depending on the scientific value of the collection and the availability of resources to support the additional work.
    - NIDDK-CR requires that the label stock used is rated to withstand extreme laboratory conditions and remain readable and adherent to the vials or containers throughout their expected life. For example, study groups should consider that labels and label information must remain on the vial throughout any anticipated processing, storage, and downstream use, such as heat blocks, water baths, xylene and alcohol processing, etc. Also, the NIDDK-CR Biorepository recommends cryogenic barcode labels that adhere to frozen vials and are rated for long-term storage in ultra-cold units, such as mechanical freezers (-80°C), liquid nitrogen freezers (approximately -180°C), and dry ice transportation.[3] NIDDK-CR Biorepository will work with study groups to recommend labels based on their existing printing capabilities, provide labels, or suggest a vendor to help with label sourcing.
    - Each specimen vial should have a single label attached that does not overlap, and leaves a gap to visualize the specimen volume. All label information must be in permanent ink. It is important to note that NIDDK-CR Biorepository does not accept handwritten or non-barcoded labels, as these can introduce readability and quality control issues.
        - When using a one-dimensional (1D) barcode, the label should be applied to the vial with the barcode in a vertical orientation to avoid the barcode wrapping around the vial and becoming unscannable.
        - When using a 2D barcode that is square, the label can be placed vertically or horizontally, as long as the volume of the specimen remains visible. It is critical to confirm that there is sufficient "white space" surrounding a barcode to ensure its ability to be scanned.
    - NIDDK-CR Biorepository recommends using a simple labeling scheme and the use of the same labeling configuration on all vials for the study protocol and for multiple protocols within the same consortium. In addition, label information should comply with NIDDK-CR vial labeling requirements listed below, including inclusion of a scannable barcode (1D or

[3] Recommended labels can be acquired from different vendors, including GA International LabTAG, or Avantor ScienceCentral

2D) for the unique vial identifier, an eye-readable representation of the barcode/unique identifier, a non-identifiable, HIPAA-compliant study participant identifier that is unique per individual enrolled (i.e., not shared in a group such as a family trio), and the material type contained in the vial. Other specimen-related information, such as study group, consortium or network, site code, collection date, time of collection, associated study visit or timepoint, or material modifier, may be included on the vial label. However, NIDDK-CR Biorepository recommends that this additional information be provided separately in an electronic manifest, as this will help keep the label information as simple as possible.

- **Best Practice:** It is standard practice to inspect vial labels prior to applying them to specimen vials. This should include a visual check for formatting issues such as the print being too small, an illegible font/font cut off from the edge of the label, dark/splotchy printing, faded printing, etc., to ensure the quality of the printed information. NIDDK-CR Biorepository requires the submission of an example label or images, and that the label be tested by all parties that will be handling the specimens to ensure it can be scanned reliably. Further, to support future automation, NIDDK-CR Biorepository strongly suggests the use of standardized vials across all enrolling sites with built in barcodes linked to specimen vial information as best practice. Whenever possible, laser-etched 1D/2D pre-coded containers are favored over adherent labels. This is particularly beneficial for specimen storage at ultra-low temperatures, especially when containers are handled or stored using automation systems. Examples of well-labeled vials and barcodes, and of insufficient or illegible labeling are provided in **Figure 1**.

5. **Budgeting for Archival Set Temporary Storage and Eventual Submission:** NIDDK-CR policy supports research by providing a source of specimens derived from NIDDK-funded clinical cooperative agreements or consortia for future research uses. This policy maximizes cost-efficiency and value by housing only specimens that are likely to be useful to the broader research community. According to NIDDK and NIDDK-CR policy, NIDDK-CR will cover the costs to transfer approved specimen archival sets to the NIDDK-CR Biorepository. This includes the provision of all the necessary materials to package and ship vials (except the dry ice). NIDDK-CR reserves the right to reject any collection if it is not considered representative of the enrolled population or scientifically valuable.
    - As previously noted, NIDDK-CR does not cover expenses related to collecting the specimens or temporary storage before transferring them to the NIDDK-CR Biorepository, for example, costs associated with identifying a temporary storage facility, reviewing documentation, processing specimens, packaging, etc. It is important to note that some commercial warehouses or laboratories may charge anywhere from $1.00 up to $8.00 or more per vial for temporary storage and retrieval services, and these costs should be factored into the budget estimates. For costs not covered by NIDDK-CR, study groups may estimate dedicating approximately 2.5% of their budget for costs associated with setting aside a representative set of specimens and consider other supporting information provided by their central facility, core laboratory, or data coordinating contracts for accurate estimates. **Table D** provides a list of considerations for planning a budget when designing an archival set for the eventual submission into the NIDDK-CR Biorepository.

## B. Archival Specimen Collection and Preservation

According to NIDDK sharing policy, NIDDK-funded clinical cooperative agreements or consortia should plan to set aside a portion of the collected specimens for later distribution to the broader research community. Collecting and preserving the portion of specimens that will become the archival set for later distribution requires deliberate planning. Similar to when designing the archival set, this planning should include decisions about specimen processing and temporary storage. Below, we provide detailed guidance on aspects study groups should consider when planning a collection for eventual archival into NIDDK-CR, with particular attention to processing and storage at the time of collection.

1. **Standard Procedures:** NIDDK-CR requires that study groups develop and submit laboratory manual of operations (L/MOP) drafts during the study protocol registration and onboarding request approval process. L/MOP processes should be standardized across enrolling sites within a study protocol, and when possible, among protocols from the same consortium, network, or center.
    - Although collection and preservation methods will vary depending on the material type and their planned downstream application, study groups should employ standardized methods for the collection and preservation of specimens across enrolling sites and develop L/MOP using broadly accepted specimen collection and processing standard operating procedures (SOPs).
    - Standardization and optimization of pre-analytical variables that occur prior to specimen testing are critical regardless of the specimen source. Factors such as draw order, processing, freezing method, storage conditions, and thawing protocols need to be carefully controlled and documented to minimize the introduction of potential artifacts and ensure reliable results that are consistent across sites and reproducible. The details (e.g., time and protocol utilized) in this stage should be well documented to help determine any impact on fitness for purpose and future secondary use.
2. **Temporary Storage:** NIDDK-CR refers to the preservation of the specimen material type collected for a limited period, between excision from the body and pre-processing, testing, or transfer to long-term storage, as temporary storage. Temporary storage may include local, site-level temporary storage and/or an external centralized location, such as a central laboratory, biobank, or repository, that helps temporarily store, aliquot, process (pre-analytical pre-processing), test, and distribute specimens, including those earmarked for the NIDDK-CR Biorepository.
    - NIDDK-CR requires that study groups plan for temporary storage prior to sending specimens to NIDDK-CR Biorepository, ideally, short-term local storage, followed by storage at a centralized location. Study groups should plan to have adequate and appropriate storage facilities to store and maintain the collection throughout the study's duration. Archival plans should include the contact information for the centralized temporary storage facilities that can provide discrepancy resolution as specimens are transferred to the NIDDK-CR Biorepository, as well as provide additional details about specimen collection, processing, and storage conditions.
    - When developing temporary storage plans, including local site and centralized laboratory or biobank/repository, study groups should pay particular attention to

storage conditions and temperature ranges at which specimens will be collected, processed, stored, and transferred. It is widely acknowledged that fluctuations in temperature during transport or warm storage conditions, even for a short period, 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 specimen material acquisition through processing and storage. This will avoid the introduction of unnecessary artifacts in downstream analyses. Study groups should also consider that temporary storage should be accounted for in budget planning and the development of standardized procedures and operational manuals. Recommended storage temperatures by material type are provided in **Table E**.

- **Best Practice:** To ensure the integrity of the specimens, they should be preserved as quickly as possible after removal from the research participant. In alignment with best practices, NIDDK-CR recommends that specimens be stored in appropriately sized boxes that are validated and tested for ultracold storage at the time of collection. Also, it is recommended that vials be placed in boxes with tight-fitting lids and without leaving spaces to ensure vials do not become dislodged during handling and transit.[4] While completely sterile conditions may not be required for many specimen collection and processing approaches, adequate consideration should be given to the cleanliness of instruments, surfaces, and equipment used in specimen processing and handling to ensure materials are free from potential contamination. For example, RNA is particularly sensitive to RNAses, which may be present on tools and surfaces that have not been properly cleaned or sterilized. Contamination of microbial DNA may interfere with downstream applications, and similarly, endotoxin contamination may affect downstream functional immunological assays. Additionally, microbial, viral, and parasitic contamination can potentially compromise specimen stability through accelerated degradation, potentially affecting specimens before storage or during cooling or warming. According to the Recommendations for Repositories[4] , when disposable instruments are used, every specimen should be handled with fresh instruments. 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.

## C. Submitting Specimens (Materials) to NIDDK-CR Biorepository

NIDDK sharing policy (Supplement to the 2023 NIH Data Management and Sharing Policy) expects selected studies, typically NIDDK-funded clinical cooperative agreements or consortia, to submit specimens to NIDDK-CR using the same timelines for the scientific data they generate in accordance with their approved Data Management and Sharing (DMS) Plans. According to NIDDK-CR policy, practices, and procedures, study groups required or planning to submit specimens to NIDDK-CR Biorepository should plan to transfer subsets of the specimens at regular intervals. These intervals should be based on the rate of participant enrollment accruals and take into consideration other factors, such as temporary and long-term storage facilities and transportation logistics. Transfer of specimens to NIDDK-CR Biorepository requires advance planning and approval of the archival plan

[4] ISBER Best Practices: Recommendations for Repositories (5th Edition, 2023).

and pilot shipment. Below, we provide detailed guidance on aspects study groups should consider when planning for the submission of specimens into NIDDK-CR.

- **Document Clearance:** In accordance with NIDDK-CR policy, before specimens can be submitted to the NIDDK-CR Biorepository, each study protocol must be approved to deposit specimens. NIDDK-CR has implemented procedures to facilitate the submission and approval process of these documents via the Resources for Research (R4R) website. All newly registered study protocols are required to provide study metadata via the NIDDK-CR R4R website rather than via email.
- **Pilot Shipment:** After study protocol document clearance, proposed archival set approval, and once enrollment has begun, NIDDK-CR Biorepository recommends scheduling a pilot shipment with a subset of each specimen type being archived, prior to sending a routine or bulk shipment of specimens. This allows the NIDDK-CR Biorepository to identify any challenges in logistics without placing a large set of specimens at risk, while also having the opportunity to review specimen labels to ensure NIDDK-CR standards are met.
- **Shipment Intervals:** It is important to note that study groups anticipating submitting specimens should consult NIDDK-CR prior to finalizing their aliquot scheme and shipment intervals, to ensure the proposed quantities to be submitted at each interval can be accepted, as there are limits to the number of samples that the Biorepository can accept each year from each study.
- **Electronic and Physical Shipment Manifests:** It is expected that for each shipment of biological material, the study group will provide the NIDDK-CR Biorepository with an electronic copy of the shipment manifest prior to the material being physically shipped to the Biorepository. A physical manifest must accompany the actual shipment. The metadata included in the electronic copy of the shipping manifest will be uploaded to the Biorepository's inventory management system and will ensure that the specimens are suitable for future research applications and can contribute meaningfully to scientific advancement. Note that NIDDK-CR will accept only archival sets that are representative of the enrolled population, meet established quality standards, and are deemed scientifically valuable.
    - Study groups (and sites) shipping to NIDDK-CR Biorepository are required to provide pre-notification of the shipment and attach a copy of the shipment manifest (i.e., electronic manifest) using the BSI Engage system. The pre-notification is expected to contain pertinent shipping details, including date of shipment, courier, shipment tracking number, quantity, and type of material shipped.
    - The electronic copy of the shipment manifest should be in CSV or XLSX format and contain all specimen information to be captured in the Biorepository inventory management system.
    - Per federal transportation regulations, U.S. Department of Transportation (DOT), International Air Transport Association (IATA) standards (IATA Dangerous Goods Regulations), and IATA guidelines (IATA Infectious Substances Shipping Guidelines), a physical shipment manifest must be placed in the shipping container to accompany the specimens while in transit. Study groups (and sites) shipping to the NIDDK-CR Biorepository are responsible for ensuring a physical copy is included in the container.

    - The NIDDK-CR Biorepository team will provide approved users with the credentials to access BSI Engage. Additional information and training videos on using BSI Engage and initiating a shipment, including the required information and an example electronic shipment manifest, are available on the NIDDK-CR website.
- **Specimen Integrity during Transfer:** Continuity of the cold chain during transfer of material to the NIDDK-CR Biorepository is a key consideration in maintaining specimen integrity and ensuring usefulness.[5] Additionally, the packaging and shipping of human specimens must conform to all applicable regulations and standards, including, but not limited to, DOT, IATA Dangerous Goods Regulations, and IATA guidelines. Study groups anticipating shipping specimens should consult the NIDDK Biorepository prior to finalizing their shipping approach to ensure the primary, secondary, and tertiary packaging (i.e., shipping containers) are appropriate for the material destination and courier being employed.
    - Although tolerance for freeze-thaw events is assay and material type dependent, thaws may introduce undesirable modifications or may damage specimen integrity by degrading critical molecules such as RNA, proteins, or even cause minor DNA damage, and can affect some assay results, such as methylation state or PCR.
    - **Best Practice:** In alignment with best practices, NIDDK-CR recommends that when shipping biologics, the teams should focus on strict temperature control (refrigerated, frozen, or ultra-cold), robust three-tiered packaging (primary, secondary, outer) with leak-proof/durable containers, appropriate hazard labeling (biohazard, UN 3373, etc.), sufficient absorbent material, and meticulous documentation (packing slips, tracking, emergency contacts) to maintain sample integrity, and ensuring teams comply with regulations like IATA/DOT for time/temperature sensitive materials.
    - **Additional Information Concerning International Shipments:** Shipping biological materials to and from international sites can introduce unique challenges, including intermittent and unpredictable holds at customs while shipments clear the customs and tariff processes. In addition, all potential shipments must comply with Biospecimen Security (NOT-OD-25-160), which prohibits distributing human biospecimens from U.S. persons (funded by NIH) to entities in "countries of concern" for national security reasons. To avoid risking the precious participant samples by thawing, and to reduce the risk of delayed transit, NIDDK-CR strongly recommends using a premium courier for international shipments. This helps prevent issues during transit, as their internal brokerage teams can review paperwork before pickup and suggest any necessary changes to documentation (e.g., commercial invoices with accurate and appropriate descriptions of the goods). This should lead to a more efficient clearance process. Premium couriers should also be able to re-ice shipments and maintain the required temperature if delays occur.

[5] NCI Best Practices for Biospecimen Resources, March 2016

## D. Informed Consent Language Clearance

In accordance with NIDDK-CR policy, Repository staff must verify that appropriate language is in place for the collection, storage, and distribution of resources generated from study participants who contribute to the Repository, especially language that facilitates future research use with minimal restrictions. Ideally, informed consent language is reviewed at the time of study onboarding before participant enrollment, and whenever there is a modification to the consent language that affects the collection, storage, and sharing of data and specimens.

1. Consortia must provide copies of the Informed Consent documents for each study protocol contributing resources to NIDDK-CR. A consortium may have a single protocol or multiple protocols. If multiple protocols are conducted, informed consents for each must be cleared before specimens can be accepted into the NIDDK Biorepository. Language must be consistent with current best practice and follow relevant NIH policies and recommended example language.[6,7]
    - The coordinating unit, in close collaboration with Program staff, will submit Informed Consent template drafts to the NIDDK-CR R4R website during the onboarding process for future use language clearance at least 20 days prior to submitting them for IRB review. This will allow NIDDK Repository staff to provide feedback tailored to the study, and for the Study group to respond to recommendations.
        - Study groups should submit only the Master Template for clearance, unless the protocol is not under a single IRB oversight or site-specific language relevant to the collection, storage, and distribution of data and specimens differs significantly from the Master Template. Assents and similar versions of the documents, such as translations or for various audiences, are not required for the clearance process, but may be submitted.
    - **Best Practice**: Study groups should ensure that informed consent documents clearly and transparently describe the voluntary nature of participation, the long-term storage of biospecimens and associated data at NIDDK-CR or NIH repository, and their use and sharing for future secondary research. Participants must be informed that they may withdraw from research participation at any time; however, consent materials should also clearly distinguish between withdrawal from ongoing study activities and the secondary use of specimens and data that have already been collected, which may be kept and used. When biospecimens may be used to generate new materials (e.g., cell lines, induced pluripotent stem cells (iPSCs), or other derivatives), consent language should explicitly address whether participants may request the destruction of their samples and, if so, up to what point. For these materials, study groups may ethically establish a defined threshold ("point of no return") after which derived materials cannot feasibly be retrieved or destroyed, particularly when such materials require substantial scientific investment or have been distributed to other qualified investigators. If such a threshold is adopted, it must be clearly explained in the consent and archival plan, including the rationale and any practical limitations on retrieval as appropriate. Study

[6] Informed Consent for Secondary Research with Data and Biospecimens: Points to Consider and Sample Language for Future Use and/or Sharing, Office of Science Policy, Office of Extramural Research, National Institutes of Health.
[7] NIDDK Central Repository Example Language for Informed Consents

groups should carefully consider how consent permissions will be tracked, how withdrawal requests will be operationalized, and how these policies align with NIH and NIDDK-CR expectations. Clear, prospective communication at the protocol development stage promotes respect for participant autonomy, fosters trust, and supports the responsible stewardship and long-term scientific utility of shared resources.

## Tables

***Table A - Standardized Material Type Categories for Submission to NIDDK-CR***

| Category | Material Type | Information required to be submitted with specimens |
|---|---|---|
| Biological Macromolecules | DNA | Specific type (e.g., cDNA) and mass, concentration, and elution buffer if known |
| Biological Macromolecules | RNA | Specific type (e.g., mRNA, mitochondrial RNA, RNA supernatant) and mass, concentration, and buffer if known |
| Biological Macromolecules | Protein | Origin of material and mass, concentration, and suspension buffer if known |
| Fluids | Blood | Preservative or stabilizing agent (e.g., MM tolerance test, Pax gene, preservative) |
| Fluids | Serum | Source and preservative |
| Fluids | Plasma | Source and preservative |
| Fluids | Urine | Source (e.g., 24 hr. urine, overnight urine) and preservative |
| Fluids | Stool | Preservative |
| Fluids | Saliva | Preservative |
| Fluids | Bile | Preservative and collection method |
| Fluids | Pancreatic | Preservative and collection method |
| Solids | FFPE block | Origin of material and type of staining (if any) |
| Solids | Tissue | Origin of material, then tissue type (e.g., biopsy, aspirate, remnant, core, explant, wedge) and type of staining (if any) |
| Solids | Nail clipping | |
| Solids | Tooth | |
| Solids | Dried blood spot | Origin of material |
| Cells | EBV transformed | Source and cell number |
| Cells | Fibroblast | Source and cell number |
| Cells | Buffy coat | Preservative |
| Cells | Leukocytes | Preservative |
| Cells | Lymphocytes | Source or type (e.g., B cells) |
| Cells | PBMC | Preservative |
| Cells | RBC | Preservative |
| Environmental | Water | Source |
| Environmental | Soil | Source |
| Swab | Nasal | Preservative, source, or type (e.g., cellular or solid) |
| Swab | Buccal | Preservative, source, or type (e.g., cellular or solid) |
| Swab | Urogenital | Preservative, source, or type (e.g., cellular or solid) |
| Swab | Perineal | Preservative, source, or type (e.g., cellular or solid) |
| Swab | Vaginal | Preservative, source, or type (e.g., cellular or solid) |

***Table B - Example Yields by Material Type and Archival Set Aliquoting Scheme Plan***

| **Material Type** | **Expected yield from a 10 mL blood tube (~8.5 mL of blood)** | **Common single-use volume or quantity** | **Number of vials for archival set** |
|---|---|---|---|
| Serum | 3.5 to 4.5 mL | 0.25 mL | 4 vials @ 0.25 mL<br>remainder at 1 mL/vial |
| Plasma | 3 to 4 mL | 0.25 mL | 4 vials @ 0.25 mL<br>remainder at 1 mL/vial |
| PBMC | 5 x $10^6$ to 20 x $10^6$ cells | 5 x $10^6$ cells | Viable Cells: 5 x $10^6$/vial<br>Pellets: 1 x $10^6$/vial |
| DNA | 240 µg from Fresh Blood<br>200 µg from Frozen Blood | 2 µg | 4 vials @ 2 µg<br>remainder in 2 vials |
| RNA | 12 µg | 1 µg | 4 vials @ 1 µg<br>remainder in 2 vials |

***Table C - Example Vial Types for Common Volumes and Temperature Ranges***

| **Vial Size Range** | **Temperature Range** | **Vial Description** | **Vendor** |
|---|---|---|---|
| 0.5 mL to 2 mL | -90 °C to +121 °C | - Sterile<br>- Self-standing vials<br>- O-ring and attached caps | CLEARSEAL™ ST. SCREW CAP MICROCENTRIFUGE TUBE (cuevasdistribution.com) |
| 1 mL to 5 mL | -196 °C to +121 °C | - Sterile<br>- Self-standing vials<br>- Externally threaded cap | STERILE SELF-STANDING CRYOVIALS W/ EXTERNAL CAP THREAD (cuevasdistribution.com) |
| 1 mL to 50 mL | -196 °C to +121 °C | - Self-standing vials<br>- Externally threaded cap | CryoClear™ Vials, External Thread (labdepotinc.com) |
| 1.2 mL to 5 mL | -196 °C to +121 °C | - Sterile<br>- Self-standing vials<br>- Externally threaded cap | WHEATON® CryoELITE® Cryogenic Vials, External Thread (labdepotinc.com) |
| 0.2 mL to 2 mL | -80 °C to -196 °C | - 2D barcoded<br>- Standard SBS rack configuration<br>- Suited for automated sample management systems | FluidX™ 2D-Coded Sample Tubes (azenta.com) |

### *Table D - Considerations for Setting Up a Specimen Collection and Budget Planning*

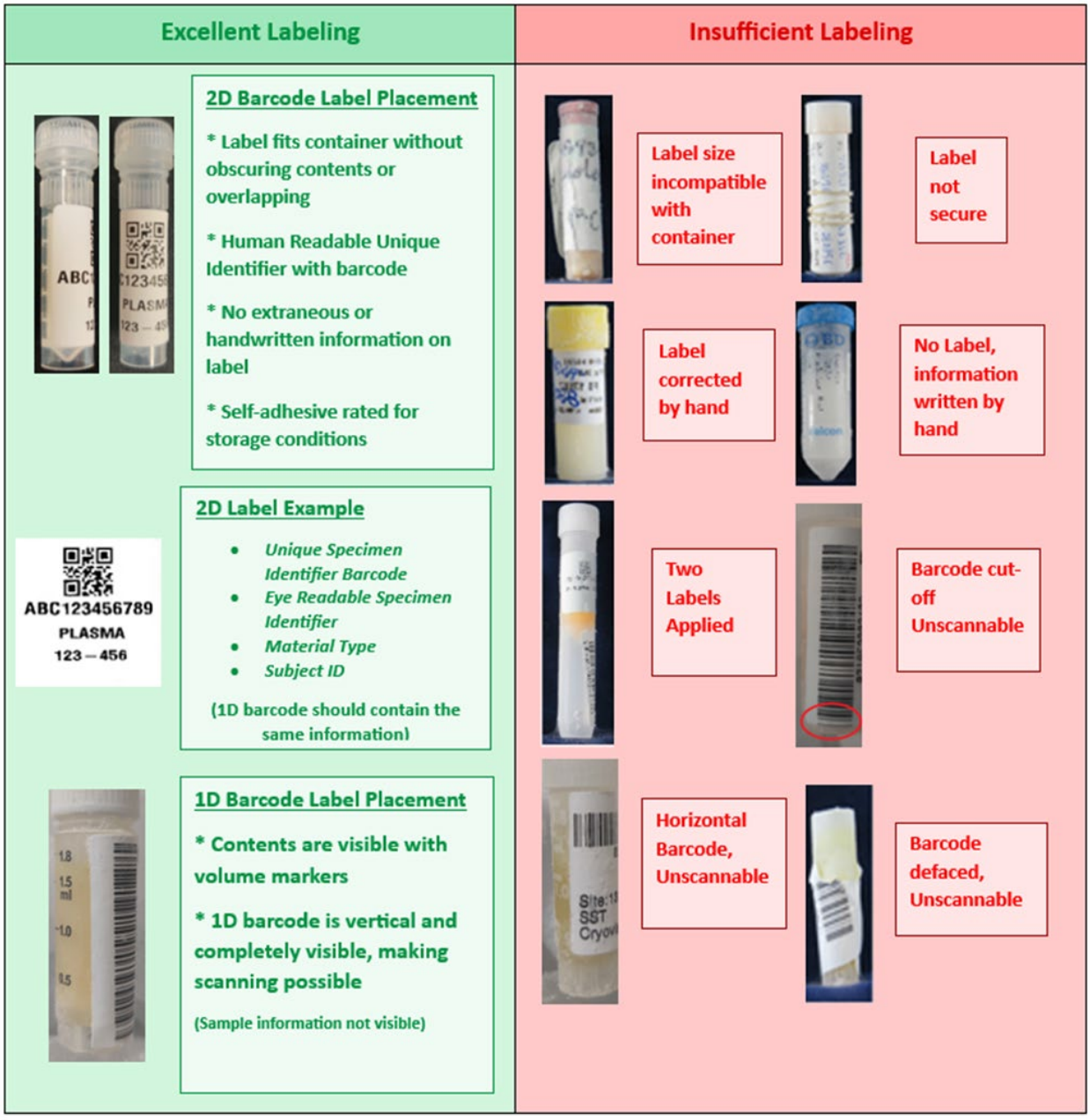
| Study Protocol Stage | NIDDK-CR | Consortium |
|---|---|---|
| **Pre-protocol Start-up** | | |
| Identify required infrastructure, facilities, equipment, and personnel | | x |
| NIDDK-CR initial protocol registration and onboarding | x | x |
| Consent form draft language review | x | x |
| Consent form generation and validation, including regulatory submissions | | x |
| Archival plan draft generation | | x |
| Archival plan review/approval | x | |
| **Specimen Collection and Processing** | | |
| Clinical lab consumables for sample collection (e.g., gloves, vacutainers, collection tubes, kitting, needles, transport coolers/totes, biohazard/sharps bins, etc.) | | x |
| Qualified and trained personnel for collection (e.g., phlebotomists, laboratory technicians) | | x |
| Specimen sorting, processing, and aliquoting | | x |
| Barcoded labels, printing supplies | | x |
| Specimen inventory management software | | x |
| Clinical lab consumables for preparation of aliquots (e.g., gloves, cryovials, pipette tips, etc.) | | x |
| Collection site temporary storage (e.g., freezer space, freezer boxes, etc.) | | x |
| **Data Processing** | | |
| Data entry and transcription (e.g., specimen collection logs, consent permissions, specimen attributes, etc.) | | x |
| Data harmonization, curation, and quality validation | | x |
| Data submission to applicable repositories for sharing (secondary use) | | x |
| **Sample Storage** | | |
| Shipment to central facility (e.g., gloves, packaging, manifests, shippers, waybill) for analyses and/or temporary storage | | x |
| Central facility accession, inventory maintenance, and analytics | | x |
| Preparation for transfer to NIDDK-CR (packaging, electronic manifests, personnel time) | | x |
| Transfer shipment to NIDDK-CR (shipper boxes and waybill) | x | |
| Long-term storage at NIDDK-CR and maintenance (accession, inventory system maintenance, sample maintenance, genetic sample maintenance, QC testing) | x | |
| **Data Storage** | | |
| Specimen inventory management software | x | x |
| NIDDK-CR public-facing Study Page content | x | x |
| Data privacy review, curation, validation, and public package creation (including 508-remediation) | x | x |
| **Post Accrual Requisitions** | | |
| Specimen inventory management, maintenance, and support | x | |
| Secondary use requisition proposal reviews and approvals | x | |
| **Specimen Requisition and Order Processing** | | |
| Laboratory consumables (e.g., gloves, cryovials, sample plates, storage boxes, new labels, etc.) | x | |
| Distribution processing and handling (quality control/assurance, aliquots, packaging, shipper boxes, dry ice, shipping manifests, etc.) | x | |
| Courier costs for requests outside the study group (e.g., shipping labels or waybill) | N/A | N/A |

***Table E - Recommended Storage Temperatures by Specimen (Material) Type***

| **Material Types** | **Storage Temperature** |
|---|---|
| Lymphocytes, PBMC, Viable Cells | LN2 Vapor (approximately -180°C) |
| Buffy Coat, Plasma, Serum | -80°C |
| Whole Blood/Blood Spots | -80°C |
| DNA, RNA | -80°C |
| Swabs | -80°C |
| Saliva | -80°C |
| Urine, Stool | -80°C |
| Non-Viable Cells/Cell Pellets | -80°C |
| Slides/FFPE Blocks | 4°C or Ambient |

## Figures

***Figure 1 – Examples of Excellent and Insufficient Vial Labeling***



## References


NIDDK-CR Policy

NIH DMS Policy

NIH Policy on Enhancing Security Measures for Human Biospecimens

Informed Consent for Secondary Research with Data and Biospecimens: Points to Consider and Sample Language for Future Use and/or Sharing

ISBER Best Practices: Recommendations for Repositories (5th Edition, 2023)

NCI Best Practice for Biospecimen Resources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