
# The BioLINCC Handbook

## Guide to Accessing the NHLBI Biologic Specimen and Data Repositories

www.biolincc.nhlbi.nih.gov

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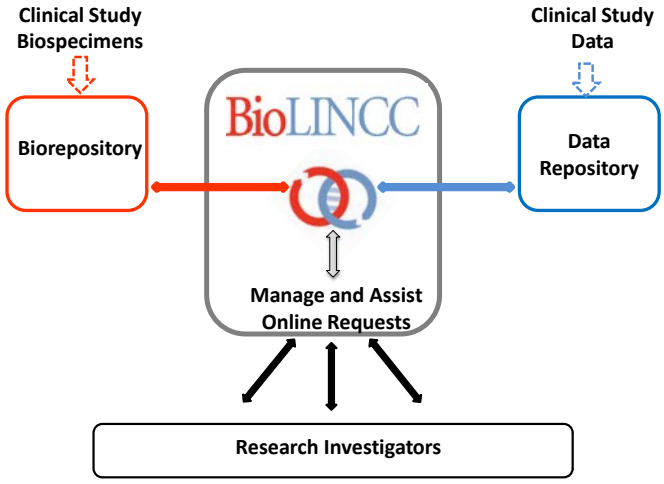



The National Heart, Lung, and Blood Institute (NHLBI) is one of 27 Institutes and Centers at the National Institutes of Health. The Institute supports basic, translational and clinical research in heart, lung and blood diseases and has a Strategic Plan structured around three goals. These goals are: Goal 1: Form to function; Goal 2: Function to cause; and Goal 3: Cause to cures. Two strategies to accomplish these goals are "t*o develop and facilitate access to scientific research resources"* and "*increase the return from NHLBI population-based and outcomes research"* (http://www.nhlbi.nih.gov/about/strategicplan/).

In line with the goals of the Strategic Plan, the NHLBI established the Biologic Specimen and Data Repositories Information Coordinating Center (BioLINCC) to facilitate access to, and maximize the scientific value of, two unique population-based scientific resources. These resources are the NHLBI Biologic Specimen Repository (Biorepository), managed by the Division of Blood Diseases Resources Transfusion Medicine and Cellular Therapeutic Branch since 1975; and the NHLBI Data Repository, managed by the Division of Cardiovascular Sciences Epidemiology Branch since 2000. Many of the clinical studies in the Data Repository have associated biospecimen collections stored in Biorepository. Figure 1.1 illustrates the organization of the BioLINCC program.

## 1.2 BIOLINCC

The mission of BioLINCC is to facilitate access to, and maximize the scientific value of, the Biorepository and Data Repository and promote the availability and use of other NHLBI funded population-based biospecimen and data resources.

BioLINCC is funded using the contract mechanism. In the first year of the contract, study datasets and documents in the Data Repository were centralized, vials in the Biorepository's electronic inventory were linked to their phenotypic data in the Data Repository, and a robust, flexible and secure web-based communication platform was established.

At the beginning of the second contract year the public web site at www.biolincc.nhlbi.nih.gov was launched to provide study specific information, a search engine and an online secure application process for data and biospecimens. The infrastructure currently supports a private website workspace to manage biospecimen and data requests and an automatic query system to collect information on publications and the requestor's experience with the BioLINCC program. Details of the communication portal are provided in Chapter 2 of this handbook.

## 1.3 BIOLOGIC SPECIMEN REPOSITORY (BIOREPOSITORY)

### 1.3.1 OVERVIEW

The mission of the NHLBI Biorepository is to acquire, store and distribute quality biospecimens to the wider scientific community using standardized processes and procedures approved by the NHLBI.

The NHLBI Biorepository contract has been managed by the Division of Blood Diseases and Resources, Transfusion Medicine and Cellular Therapeutics Branch since the mid-1970s. During the first 20 years of operation, the Biorepository acquired several large plasma, serum and whole blood collections from epidemiologic studies conducted in blood donors and transfusion-recipients. Research on these biospecimens enabled key advancements in transfusion safety including evaluation of donor screening assays for viral agents such as HIV, hepatitis B and hepatitis C, and risk estimations for transfusion-transmitted viral agents. In recent years, the use of the NHLBI Biorepository has expanded to include biospecimens collected from a variety of cardiovascular, pulmonary, and hematological studies supported by NHLBI.

### 1.3.2 AVAILABILITY OF BIOSPECIMENS

Biorepository collections are either "Proprietary" or "Open":

"Proprietary" – access to the collection is provided by the study investigators (Parent Study). A collection remains proprietary until the clinical study data are made available to BioLINCC for sharing following the NHLBI data set sharing policy timeline at http://www.nhlbi.nih.gov/funding/datasharing.htm . During the proprietary period, the BioLINCC website directs requesting researchers to the Parent Study for additional information on data and biospecimens, because that information is not yet available to BioLINCC. The Parent Study is primarily responsible for reviewing and approving these requests.

"Open" – the collection is under the custodianship of the NHLBI. This period starts when the "proprietary period" ends. The NHLBI is responsible for reviewing and approving these requests in accordance with the review processes described in this handbook.

Wherever possible, manuals of procedures and details of protocol-mandated collection and storage procedures have been obtained and are made available to the requestor through the BioLINCC website. Furthermore, many collections have undergone central quality assurance assays or have been visually inspected for apparent discrepancies between their contents and volumes as reported in inventory records vs. other information. Inventory records include information on stated material type, vial warnings, apparent hemolysis, number of thaws, additive, preservatives and special procedures or historical storage conditions. The Biorepository also has a great deal of knowledge of special characteristics and other historical information related to each collection. All of this is incorporated in the technical assessment of biospecimen requests which aims to ensure that the studies and specific vials that are selected are the best fit for the proposed research. In some cases it will be recommended that a pilot study be attempted prior to the release of the full requested number of biospecimens to ensure that the collection is compatible with the proposed assays.

Access to Biorepository collections is through the BioLINCC website at www.biolincc.nhlbi.nih.gov . Chapter 3 of this handbook provides details on accessing "Open" biospecimen collections and chapter 4 provides details on accessing "Proprietary" collections.

## 1.4 DATA REPOSITORY

### 1.4.1 OVERVIEW

The NHLBI has supported data collection from participants in epidemiology studies and clinical trials for over six decades. These data have often been sent to the NHLBI at the conclusion of the study and placed in a Data Repository. The Data Repository is managed by NHLBI staff in the DCVS Epidemiology Branch and includes individual level data on more than 540,000 participants from over 90 Institute supported clinical trials and observational studies.

A formal data sharing policy was established in 1989 to enable the datasets in the repository to be shared with qualified investigators. The policy outlined the timing of release of the data after completion of the study and provided guidelines on redacting the data set to maintain participant confidentiality. The policy was revised in 1999 to incorporate specific data release timelines, guidelines for data submission, and the data request process and the policy was approved as a formal protocol in 2000 by the NHLBI IRB. Following the establishment of BioLINCC, the protocol was again revised in 2008 and 2012 to include the process described in this document. The NHLBI IRB continues in its oversight role to annually review activities of the Data Repository and any changes to the protocol. The NHLBI Policy for Data sharing from Clinical Trials and Epidemiology Studies (http://www.nhlbi.nih.gov/funding/datasharing.htm ) describes the submission and release schedule for data sets stored in the NHLBI data repository.

### 1.4.2 AVAILABILITY OF DATA SETS

The repository data set for clinical trials generally includes the baseline, interim visit, ancillary study and outcome data, including laboratory measurements. Epidemiology study data sets

generally include all of the examination data obtained in the examination cycle, ancillary study and/or all of the follow up information available up to the cutoff time period. Repository data sets do not necessarily include raw data (such as food item data, individual electrocardiographic lead scores or itemized psychometric question responses, for example) which were processed into summary information or indices.

Data will not be provided for the repository if the investigators or NHLBI believe that they are unreliable or invalid. Released data will not contain information which could readily lead to identification of an individual participant. Study data are deleted or collapsed as necessary to provide this confidentiality. Data from research participants who refused to permit the sharing of their data are deleted from the repository data set. Researchers requesting repository data should be aware that although they should be able to approximate published study findings, exact replication of previous manuscripts may not be possible in some cases.

The repository contains the data and documentation as submitted by the Parent Study. Requestors will be provided with this complete packet of information. The repository was not the original coordinating center and may not be able to provide additional information on study methods, data handling decisions that were made by the Parent Study, or provide additional documentation which was not included in the data set as submitted. Wherever possible, BioLINCC will attempt to assist researchers with data-related queries; however, there are studies in the repository which are very old or where original study personnel are no longer available and additional information cannot be obtained. Chapter 3 provides information on accessing datasets in the Data Repository.

## 2.0 THE BIOLINCC WEBSITE: STRUCTURE AND FUNCTION

### 2.1 OVERVIEW

The BioLINCC website is accessed at www.biolincc.nhlbi.nih.gov.

This website is the primary interface with the NHLBI Biologic Specimen and Data Repositories Information Coordinating Center (BioLINCC). The system is comprised of two levels: public information which is available to all users, and a private workspace which is available to registered users.

The public website provides a wealth of information on historical NHLBI clinical and epidemiologic studies which have either data or biospecimens in the NHLBI repositories, including study summaries, references, and study operational documents. This information is provided in the form of searchable study web pages. More in-depth search functions of all material archived on the website is also available. Additional resources include guidelines and recommendations for building new biorepository collections, links to information on the preparation of study datasets which are suitable for use shared resources, BioLINCC forms, templates and flowcharts, and a news feed of recent additions and updates to the posted collections.

Visitors to the BioLINCC website who wish to access the full functions of the site are asked to register. Registration is quick and free, and provides access to the private workspace features of the site. Registration is required in order to request resources from the NHLBI Biologic and Data Repositories. Once a request has been submitted, communications and document

transmissions between the researcher and BioLINCC are handled electronically through the secure website request interface.

## 2.2 THE BIOLINCC HOME PAGE – PUBLIC INFORMATION


### 2.2.1 MAIN MENU

The main menu on the left side of the home page provides navigation to the various sections of the website. Of primary interest to many users is the **Open Studies** section, which is where information and items related to the bulk of biorepository/data repository are stored. Open Studies have completed their Proprietary restriction phase and are available for request through the BioLINCC website, undergoing BioLINCC review procedures. From the Open Studies section, visitors may browse the full list of **Open Study Dataset and Biospecimen** collections or learn about available **Teaching Datasets** which have been developed as educational tools. Also from this section, researchers whose existing data set use agreements are expiring may **Renew Existing Data Set Agreements**. From time to time, this section also contains links to current funding opportunities which may be available for the use of Open BioLINCC resources.

The second section within the main menu provides information on **Other Available Resources**. These resources are not maintained by BioLINCC but are available for request though external sites.

The third section within the main menu is for use by Parent Study researchers who are interested in **Submitting New Collections** for use as shared resources. This section includes a link to where BioLINCC registered users may **Register to Submit a New Biospecimen Collection.** This section also has a link to information on **Preparing and Submitting Data Repository Datasets**, which includes links to NHLBI-hosted information on Institute guidelines and policies.

The fourth section within the main menu, **About BioLINCC**, includes links to **FAQs**, a **Glossary** of terms used in BioLINCC documents, and **Reference Documents** such as the BioLINCC Handbook, the Research Materials Distribution Agreement (RMDA) and other document templates.

The fifth section within the main menu, **Proprietary Studies**, points to information on the request process for biospecimens stored within the NHLBI Biorepository for studies which are still in the Proprietary Phase. Although BioLINCC provides assistance in the fulfillment of approved requests in this phase, the request review is conducted by the Parent Study of the proprietary collection, following their established procedures.

The sixth section within the main menu is a link to allow visitors to submit emailed **Questions/Comments** about BioLINCC.

There is a seventh section within the main menu, but this section is only visible to registered users. **My BioLINCC** provides access to account information and to submitted and saved requests.

### 2.2.2 LOG-IN/REGISTRATION

Visitors wishing to request biospecimen or data resources, renew existing data set agreements or register to submit a new biospecimen collection must become registered users in order to access these private workspaces. The Log-in/Registration link is located on the upper right part of the Home Page. Registrants are asked to provide their name, institutional affiliation, email address and telephone number, and to select a username and password. They may also wish to provide their address and fax number. Upon clicking the Register button at the bottom of the page, the request will be sent to BioLINCC. A confirmation email is auto-generated and sent to the email address provided by the user. This email contains a link, which, once clicked, will confirm and complete the registration.

Registered users log into the BioLINCC site using the Log-In/Registration link. Requests for password/username reminders may be submitted though the log-in webpage.

Once logged in as a registered user, a sixth section within the main menu will appear. **My BioLINCC** allows users to view their saved and submitted requests and manage their BioLINCC registration account.

### 2.2.3 STUDY WEBPAGE SEARCH

The study webpage search utility, located in the lower central part of the BioLINCC home page, provides a way to filter the study resources that are displayed, based upon parameters selected via the tabs and drop-down selections and/or key words provided by the user. This search utility provides results based upon collection type (data, specimens or both), study period (open or proprietary), specimen material type, keywords as drawn from the NIH Clinical Trials summary (www.clinicaltrials.gov), and other main study properties. User-supplied text for searching is matched against the contents of each study web page. Associated study documents are not searched using this utility (but see section 2.2.4, Full Website Search).

### 2.2.4 FULL WEBSITE SEARCH

The full website search, located in the upper right corner of the BioLINCC home page, provides an interface for more detailed searches across the full searchable contents of the BioLINCC website. This search is more powerful than the study webpage search, and offers advanced search capabilities. Because of the volume of associated documents posted on the BioLINCC site, this search may return a very large number of hits depending on the specificity of the search terms used. It is most useful as a secondary tool to search for studies which may have examined or collected very specialized types of data.

### 2.2.5 NEWS FEED

News items are posted to announce the availability of new studies or study updates, and to provide notifications of special events and funding opportunities.

## 2.3 MY BIOLINCC – THE PRIVATE WORKSPACE AREA

Registered BioLINCC users gain access to the private workspace area for request submission and processing. Resource request types include BioLINCC Open Studies, Teaching Datasets, Data Renewal Requests (for expiring existing data agreements), and Proprietary Studies. Registrations and processing functions for applications to submit new biospecimen collections are also included in the private workspace area. Upon registration, an additional menu item, My BioLINCC, appears as an option in the Main Menu. Selecting My BioLINCC brings up a new screen which contains tabbed links to the user's submitted requests and to requests which have been saved but not yet submitted for processing. From these listings the user may bring up the information from each request, including the full text of the submitted request and any attachments, and the comment page which is the main communication medium between the user and BioLINCC staff. The comment page is a cumulative record of the request discussion.

Upon submission of any request, the user receives an automatic email confirmation of the submission, including a direct link to the request comment page as well as information on the next steps. Users and BioLINCC staff also receive notification emails when the request or

comment pages are updated; these emails also contain direct links back to the specific request workspace.

Registered users only have access to requests that they have initiated, unless the individual who submitted the requests provides specific permission to add an Authorized User. This function, as well as the ability to create a printable PDF of the submitted request, or to review and approve the findings of a BioLINCC specimen search, may be accessed via the Request Actions button near the upper right of the submitted request pages.

### 2.4 WEBSITE TECHNICAL INFORMATION

The BioLINCC website was developed using an open source technology stack to reduce costs and simplify interoperability with existing data systems. The SUSE Linux operating system was selected for its excellent performance and security. Apache was selected as the web server for its well-known capabilities and performance. Similarly, the PostgreSQL database was chosen for its capabilities and scalability, and Django as the implementation framework. Django is a high-level Python Web framework that encourages rapid development and dictated the choice of Python as a programming language for implementation.

## 3.0 REQUESTING BIOSPECIMENS AND DATA IN THE OPEN PERIOD

### 3.1 OVERVIEW

The BioLINCC website at www.biolincc.nhlbi.nih.gov is the interface for all applications for biospecimens and data stored in the NHLBI Biologic Specimen Repository (Biorepository) and the NHLBI Data Repository. There are three types of applications:

1. Biospecimens and vial characterization data (no associated research dataset available)
2. Research datasets
3. Biospecimens and associated research datasets

Biospecimens and datasets are provided free of charge to qualified investigators, with the exception of the cost of shipping biospecimens to the testing facility. Biospecimens are only made available if funds are available to perform the research. Table 1 summarizes the supporting documentation requirements for each application type.

**Table 3.1: Documentation Required Based on Application Type**

| Supporting Documentation Requirement | Biospecimens and vial characterization data | Research dataset | Biospecimens and associated research dataset |
|---|---|---|---|
| Summary of research plan (protocol) | Required | | |
| IRB review (from applicant's institution) | Written approval from the requestor's IRB must be submitted stating that the IRB has either a) performed a review of the project and issues an approval, or b) declared that the research project is exempt from review. | For the majority of studies, written approval from the requestor's IRB must be submitted stating that the IRB has either a) performed a review of the project and issues an approval, or b) declared that the research project is exempt from review.<br><br>A few studies require full or expedited review and an exemption statement cannot be accepted. This requirement is noted on the Study Page. | |
| Curriculum vitae | Required | Optional | Required |
| On-line request form | Required | | |
| Research Materials Distribution Agreement (RMDA) | Required; components are generated by the website automatically | | |

All requests undergo a review process that includes the qualifications of the researcher, availability and appropriateness of the biospecimens/data for the proposed research, and compliance with human subject regulations. Section 3.3 describes the review of biospecimen requests and Section 3.4 the review of dataset requests.

## 3.2 STEPS FOR REQUESTING BIOSPECIMENS AND DATA IN THE OPEN PERIOD

Requests are made through the BioLINCC website at www.biolincc.nhlbi.nih.gov .

### STEP 1 – SEARCH AND REGISTER

The researcher may use the BioLINCC website keyword and search functions to identify a study or studies which may have suitable resources for the proposed research. Alternatively, the researcher may proceed directly to the target study page if already known. At the bottom of the study web page is a Request button. The researcher must be logged in as a registered user on the BioLINCC site to submit a request; if not logged in, clicking on this button will open a prompt for log-in or registration.

If the researcher is unable to identify suitable resources through searching, a general Availability Request may be submitted from either the Open Studies or the Study Datasets and Biospecimens main web pages, and BioLINCC staff will assist.

**STEP 2 – REQUEST SUBMISSION**

The first task in opening a new request is to specify whether the request is for study datasets, biospecimens, or both, as the request forms vary slightly between the three request types.

**Requests which are for data only** are the most straight-forward. The researcher is prompted for information on the study protocol or proposed research plan and for the data security measures which will be utilized. The researcher is asked to upload the IRB approval/waiver statement for the proposed research. Once these documents are submitted, the request is forwarded to the NHLBI DCVS for review and approval. Approved requests require an executed Research Materials Distribution Agreement (RMDA) before data can be transferred. This document is generated by the website based upon information provided by the requestor, and is transferred electronically between the signatory parties as PDF attachments to the request. Data from most studies are transferred to the requestor as secure transfers through the website. Data from a few studies are transferred as CDs which are shipped to the requestor from the study coordinating centers upon request approval. Data transfers for requests which also include biospecimens are made after the biospecimen component has been reviewed and approved. A single RMDA is generated for both components.

**If biospecimens are included in the request**, the researcher is asked to provide the following information:

- Request name
- Institution type (non-profit or commercial) and financial support information
- Study requested
- Number of specimens
- Material type
- Minimum volume (or DNA mass)
- Optimal volume (or DNA mass)
- Specimen requirements (e.g., preservatives, additives or other specimen requirements)
- Subject characteristics (selection criteria for the subjects providing specimens)
- A description of the request, including a summary of proposed research aims
- Analytes to be tested
- Type of assay/platform
- Justification for the number of biospecimens being requested
- Whether the materials would be used to support a commercial purpose
- Whether the requestor was an investigator with the original Parent Study
- Comments
- Formal study title, PI and approved user names and institutional information for the eventual generation of the Research Materials Distribution Agreement

The requestor is encouraged to attach the research study plan, the investigator's CV and the IRB approval/waiver statement as early as possible in the request process. Both the study plan and CV will be required prior to final review. Evidence of IRB review will be required prior to release of biospecimens – note that although IRB waivers may be acceptable for many biospecimen requests-only requests, expedited or full IRB review and approval may be required for requests involving certain study datasets. Specific datasets which require IRB review and approval are noted as such on the BioLINCC study web page.

BioLINCC staff performs a preliminary search for suitable biospecimens based upon the information provided in the request. Researchers are encouraged to be as specific as possible in their description of the search selection criteria, and to avoid the use of abbreviations and acronyms in their specifications. There may be dialogue between the researcher and BioLINCC staff to refine and finalize selections according to resource availability.

Requests that are inactive for three months will be administratively closed.

**STEP 3 - REQUEST FINALIZATION**

**For requests which are for data only**, the request is finalized when all required documentation is submitted for review by the NHLBI.

**If biospecimens are included in the request**, upon the finalization of the search (see STEP 2), and acceptance of the search results by the researcher, the request is formalized. Vials are put on temporary hold for the requesting researcher and the request is reviewed to determine the "impact" of the request on the collection (see Section 3.3.2) and who will perform a scientific review.

Applicants may request that the biospecimens be reserved for six months or until a funding decision is obtained, whichever comes first. The decision to reserve biospecimens will take into consideration the "impact" of the request on the collection (see Table 3.2). It is the responsibility of the applicant to update BioLINCC on the status of their funding decision during the six month reservation period. Requests will be administratively closed if no update is received.

## 3.3 REVIEWING BIOSPECIMEN REQUESTS

### 3.3.1 OVERVIEW

For biospecimen requests, the review takes the following guidelines into consideration:

- Investigators must have funding and adequate facilities and expertise to perform the proposed research.

- Requests for unique and limited biospecimens will undergo rigorous review, and proof-of-principle pilot testing may be required. Biospecimens in this category will not be made available for exploratory research protocols.

- Special justification may be required for the release of unthawed specimens if previously thawed aliquots are available. As part of the review process, alternative recommendations will be made if another, more abundant biospecimen collection may be superior or equivalent for the proposed research.

- Use of the last aliquot for a subject/material type/draw date may require approval by the NHLBI Division that sponsored the Parent Study.

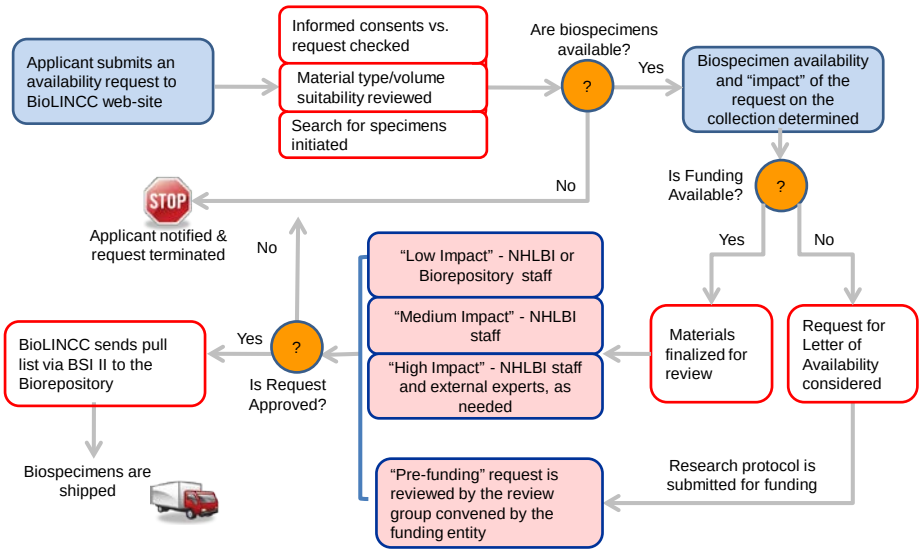
- Evidence that the proposed assays have been validated as sensitive enough and reproducible enough for the study is required. If the study itself is an assay validation, a pilot study using a subset of the requested specimens may be required.

The review process for biospecimen requests is illustrated in Figure 3.1. The two review options are:

- BioLINCC coordinates the scientific review of the proposed research plan. This is typically used when the applicant has existing funding to perform the proposed research.

- A funding group performs the scientific review of the proposed research plan. This is typically used when the applicant is searching for biospecimens prior to submitting an application to a funding group. Of note, documentation of the funding group's scientific review is required if funding is obtained.

**Figure 3.1: Streamlined Workflow for Biospecimen Requests**



Irrespective of the path followed, the review of a biospecimens request must include the following:

- Ethical considerations including consistency with the terms of the informed consent and compliance with human subjects and HIPAA regulations
- Availability and technical suitability (e.g., appropriateness of material type) of the requested biospecimens
- Scientific approach:
  - Significance and appropriateness of the proposed research
  - Availability and impact of the request on the biospecimen collection
  - Design of the proposed research
  - Qualifications of investigator(s) to do the research

### 3.3.2 ETHICAL, MATERIAL/VOLUME SUITABILITY AND "IMPACT" REVIEW

Ethical and suitability reviews are conducted by BioLINCC and Biorepository staff concurrently with the search for biospecimens. At initiation of the search BioLINCC staff reviews the research plan against the informed consent document restrictions to ensure the research is acceptable. Investigators are notified immediately if the research plan is not acceptable and the search is terminated. Alternative biospecimen resources which do not have consent restrictions for the proposed research will be suggested if available.

Following identification of appropriate biospecimens, an assessment of the availability and impact of the requested samples on the collection is prepared by BioLINCC staff and a technical review is performed by Biorepository staff. The technical review determines if the selected specimens (including volume/concentration) are suitable for the proposed research protocol.

Upon acceptance by the requestor of the final search results, BioLINCC staff creates an availability report by incorporating supplemental information regarding existing numbers of aliquots and sample volumes. The availability report is used to determine the request "impact" score that a request has on the collection. Table 3.2 includes the definitions, request restrictions and the review options for "low impact", "medium impact" and "high impact" requests. The elements taken into consideration in determining "impact" include historical use of the collection, the material type, volume remaining, potential for generating additional aliquots, expanding the material, and the availability of similar vials (i.e., the resource is not unique to the requested collection, and other lower-impact collections could be used).

**Table 3.2 "Impact" Score: Definitions, Request Restrictions and Review Options**

| Impact Score | Definition | Request Restrictions | Review Options |
|---|---|---|---|
| Low Impact | abundant biospecimens<br>*abundant: the collection can support more than six new requests based on historical use and/or other collections can support similar research* | Can be used for exploratory research<br>Letter of Availability can be provided and a six month hold requested. | NHLBI or Biorepository staff with expertise in the scientific area, or the funding group performing the scientific review |
| Medium Impact | unique and limited biospecimens<br>*unique and limited: the collection can support four to six new requests based on historical use and no other biospecimens are available* | May be used for exploratory research questions but pilot studies may be required<br>Letter of Availability and hold requests will be considered on a case by case basis | NHLBI staff with expertise in the scientific area and knowledge of the Parent Study, or the funding group performing the scientific review |
| High Impact | unique and very limited resource<br>*unique and very limited: the collection can support three or fewer new requests based on historical use, last vials may be included and no other biospecimens are available* | Not available for exploratory research<br>Letter of Availability and hold requests are granted only in exceptional circumstances | NHLBI staff with expertise in the scientific area and knowledge of the Parent Study (external experts may also be used), or the funding group performing the scientific review |

### 3.3.3 SCIENTIFIC REVIEW FOR REQUESTS WITH EXISTING FUNDING

If the researcher has existing funding at the time of the request, the request undergoes a review coordinated by BioLINCC. BioLINCC and Biorepository staff review the submitted documents for:

- The completeness of the request. The investigator is prompted via email for missing or incomplete documentation. If the submitted research protocol is determined to be incomplete, the investigator will be prompted to include the missing information before it will be sent onward for a scientific review.
- The suitability of the selected material types, volumes and proposed assay methods
- The appropriateness of the number of biospecimens requested. For requests with a statistical analysis aspect, BioLINCC statistical staff will attempt to replicate the sample size and power calculations (using calculations appropriate for the proposed statistical analysis approach). Alternative analytic approaches may be suggested, if appropriate. Some requests do not entail a statistical component and formal sample size calculations are not

necessary; however, the requestor is still required to document the rationale for the number of specimens requested.

This review is designed to ensure that all the required documentation has been submitted, that the research protocol is technically feasible and the sample size is adequate to answer the research questions(s).

Upon completion of the BioLINCC and Biorepository review, the NHLBI BioLINCC COR assigns a primary NHLBI reviewer based on the "impact" score as described in Table 3.1. The reviewer is notified via email and logs in to BioLINCC to complete the review of the materials posted by the investigator and the summary documents of the final BioLINCC and Biorepository. These are made available in the private BioLINCC website Voting Tab.

All scientific reviews use the following criteria. Reviewers are asked to comment on each topic:

- Significance of the Research Question
- Does the project address an important problem or critical barrier to progress in the field?
- If the goals of the project are achieved, will scientific knowledge, technical capability, and/or clinical practice be improved?
- If the request is considered "High Impact" (i.e. the biospecimens are unique and limited):
  - Does the proposed research protocol warrant the use of valuable and limited biospecimens? [Note: "High Impact" requests require a corresponding "high impact" scientific question and outcome. Valuable biospecimens may not be used to perform exploratory research.]
  - Should this request be reviewed by external experts? Reviewers are asked to provide the names and contact information of external experts they consider appropriate for the request.
- Approach
  - Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the project?
  - Are the BioLINCC and Biorepository reviews regarding suitability of biospecimens and sample size acceptable?
- Qualifications of the investigative team
  - Are the investigators qualified to perform the proposed research?

The results of the review are posted to the BioLINCC Voting Tab. A request may be approved, denied or deferred. The applicant is notified of the decision. A summary of the review will be provided to the applicant if the request is denied or deferred.

### 3.3.4 SCIENTIFIC REVIEW PERFORMED BY A FUNDING GROUP

If the researcher does not have funding to perform the proposed research, the request undergoes the initial ethical, suitability and availability review described in Section 3.3.2. If the funding application is successful, the researcher will be asked for documentation indicating that funding was obtained and that a scientific review covering the elements described in Section 3.3.3 has been performed. The NHLBI BioLINCC COR will determine if the documentation adequately addresses the elements of the scientific review or if a second scientific review is needed.

### 3.3.5 RESEARCH MATERIAL DISTRIBUTION AGREEMENT (RMDA)

Upon acceptance of the application for the biospecimens, the investigator will be instructed to complete a Research Material Distribution Agreement (RMDA) generated by BioLINCC staff and provide documentation of the IRB review of the research. This RMDA will be downloaded by the requesting investigator, completed, signed, and re-attached as a scanned PDF to the application. The NHLBI BioLINCC COR signs the RMDA as the NHLBI representative. If the request includes a dataset, the applicant must follow the IRB requirements for obtaining the data (See Section 3.4.1).

Upon completion of all the review steps and submission of the required documentation, BioLINCC request that the Biorepository ship the requested biospecimens.

## 3.4 REVIEWING REQUESTS FOR DATA SETS

### 3.4.1 OVERVIEW

All data reviews are coordinated by BioLINCC and are performed by the NHBLI Data Repository Director. The review includes:

- Appropriateness of the proposed research for the dataset(s) being requested
- Completion of the IRB requirements to obtain the datasets.

Requests that include datasets from studies in the Open Period must have IRB approval (waiver, expedited review, convened review). Some datasets require that the researcher's IRB provide an expedited (Chairman) or convened review for the proposed project. In these cases, an IRB approval is needed because although obvious identifiers have been redacted, the wealth of individual level data that remain (demographic, anthropometric, medical history, personal history, outcomes) means that the possibility of direct identification of a study subject cannot be eliminated.

### 3.4.2 DATASET REVIEW COORDINATED BY BIOLINCC

The materials posted by the investigator are centralized under a Voting Tab on a restricted area on the BioLINCC website. The NHLBI review is performed online by the NHLBI Data Repository Director.

Upon approval of the request, the investigator will be instructed to complete a Research Material Distribution Agreement (RMDA) generated by BioLINCC staff. This RMDA will be downloaded by the requesting investigator, completed, signed, and re-attached as a scanned PDF to the application.

In almost all cases, the datasets and associated documentation are posted in a packet which may be accessed and downloaded via a secure link within the investigator's BioLINCC request. In a few cases, upon request approval and receipt of the executed RMDA, BioLINCC notifies the study coordinating center which provides the data and documentation directly to the investigator via a mailed CD. In these cases, the requestor will be asked to confirm the preferred shipping address.

## 4.0 APPLYING FOR RESEARCH RESOURCES IN THE PROPRIETARY PERIOD

The NHLBI Biorepository contains biospecimen collections from studies which are in the Proprietary Period, a period of time in which access to the biospecimens is managed by the Parent Study before being made available for sharing with the wider scientific community. Access to these biospecimens by qualified external researchers may be possible according to study-specific policy. During the Proprietary Period, BioLINCC does not have the complete study data set and is therefore unable to determine availability of biospecimens or assist with biospecimen selection. Because BioLINCC does not have access to study data in the Proprietary Period, researchers who wish to access these data must contact the Parent Study to request these files.

Proprietary Period study names and coordinating centers/websites are posted on the BioLINCC website. Information on the request process is provided here and on the Proprietary Period web page. Please note that distribution of biospecimens from studies which have not yet completed their collection phase is generally restricted to Parent Study investigators. The restricted status of these collections is indicated in the Proprietary Period study name listing.

Requests for biospecimens in the Proprietary Period must be approved by the Parent Study. In addition to any requirements imposed by Parent Study-specific policy, the NHLBI requires that the Parent Study review includes an assessment of the following elements:

- Significance and appropriateness of the proposed research
- Design of the proposed research
- Qualifications of the investigator(s) to do the research
- Availability of funding appropriate to the scope and duration of the research
- Availability and suitability of study biospecimens to the research plan
- Ethical and legal considerations including consistency with the terms of the informed consent and compliance with human subjects and HIPAA regulations

After a request has been approved by the Parent Study, the remainder of the requisition process is managed through the BioLINCC web site. The following elements are required and should be obtained before placing the request in BioLINCC:

- The Parent Study Approval form (available as a downloadable PDF from the BioLINCC website) must be completed by both the requesting investigator and the Chair of the Parent Study Committee authorized to approve a request.

- An electronic manifest of the specific biospecimens which have been selected by the Parent Study for release to the requestor. This manifest must include information which allows the linkage of the biospecimens to the NHLBI BSI inventory system. The Parent Study will be provided access to their current complete inventory through BioLINCC.

- The requesting investigator's full or expedited IRB approval for the proposed research.

- A FedEx account number to pay to ship the biospecimens to the research facility.

Upon receipt of the elements listed above via the BioLINCC website Proprietary Period Request page, BioLINCC staff will review the submitted elements. The electronic manifest which was generated by the Parent Study and uploaded by the requesting investigator will be compared to biospecimens in inventory at the NHLBI Biorepository. A BSI Inventory Confirmation Report will be generated by BioLINCC staff which will list the biospecimen matches and mismatches (if any) and supplemental information as recorded in the BSI inventory such as material type, volume, concentration (e.g., for DNA), and other key material modifiers. The BSI Inventory Confirmation Report will be made available to the requesting investigator through the BioLINCC website. It is the responsibility of the requesting investigator to provide the BSI Inventory Confirmation Report back to the Parent Study for final sign-off of the specific biospecimens to be requisitioned. It is the Parent Study's responsibility to review the report in detail to verify the biospecimens. If the Parent Study finds unexpected information in the BSI Inventory Confirmation Report, such as missing vials, volume issues, material type problems, etc., it is the Parent Study's responsibility to generate a replacement electronic manifest which will again undergo the BSI Inventory Confirmation Report process.

Once the BSI Inventory Confirmation Report has been accepted by the Parent Study, BioLINCC staff will generate the Research Material Distribution Agreement (RMDA). This RMDA will be downloaded by the requesting investigator, completed, signed, and re-attached as a scanned PDF to the application.

To facilitate biospecimen requests in the Proprietary Period, each group (the Parent Study, the requesting investigator, BioLINCC and NHLBI staff) have assigned roles and responsibilities. These are as follows:

**Parent Study Responsibilities:**

- reviewing the biospecimen application in accordance with the Parent Study approved process

- determining availability of biospecimens

- providing the requesting investigator with an electronic manifest of the selected biospecimens to link to the NHLBI Biorepository BSI inventory

- providing the requesting investigator with the Parent Study Approval form signed by the Chair of Parent Study approval committee to document review and approval

- reviewing the BioLINCC BSI Inventory Confirmation Report generated from the electronic manifest
- providing revised documentation and manifests to the requesting investigator as needed

**Requesting Investigator Responsibilities:**

- contacting the Parent Study regarding the proposed research and obtaining the required documentation
- registering the request in BioLINCC
- submitting all necessary documentation to BioLINCC (the signed Parent Study Approval form, IRB approval/waiver for the proposed research, electronic manifest from the Parent Study, shipping FedEx account number)
- responding to questions from BioLINCC related to the request
- reviewing and approving the BioLINCC BSI Inventory Confirmation Report generated from the electronic manifest
- completing the RMDA

**BioLINCC Responsibilities:**

- reviewing the request for completeness
- notifying the requesting investigator of missing or incomplete documentation
- generating the BSI Inventory Confirmation Report from the Parent Study's electronic manifest and providing it to the requesting investigator
- following NHLBI approval, submitting the finalized biospecimen manifest as a requisition in the NHLBI Biorepository BSI inventory system

**NHLBI BioLINCC Representative Responsibilities:**

- reviewing and approving the completed request

## 4.1 STEPS FOR APPLYING FOR RESEARCH RESOURCES IN THE PROPRIETARY PERIOD

**Pre-Submission Requirements**

Contact the Parent Study to initiate the discussion regarding your request. If the Parent Study is willing to consider your proposal, you will be asked to provide them with the documentation that will be necessary for them to evaluate your research plan in accordance with both their Parent Study-specific procedures and the NHLBI minimum requirements. The NHLBI requires that the Parent Study reviews your research plan, CV, available funding to do the research, and the requested biospecimens' suitability and availability for the proposed research. Ethical and legal considerations including consistency with the terms of the informed consent and compliance with human subjects and HIPAA regulations will also be assessed. You will also

need to provide the Parent Study with your Parent Study Approval form so that they can document their review and approval.

**Submission Process**

**STEP 1 -** When the Parent Study has completed its review and has provided the electronic manifest of the biospecimens they have selected for you, you are ready to submit your request into BioLINCC. Selecting Submit Proprietary Study Request will bring up the application screen (you must be a registered user to apply, and you will be prompted to register if you have not yet done so).

**STEP 2 -** Complete the required elements of the Proprietary Study Request. These include your administrative and contact information, shipping information for the biospecimens, and a FedEx account number to pay for shipping to you. Select the name(s) of the Proprietary Study(ies) you are interested in from the drop-down box. Finally, the following documents are required attachments to your application:

- A scanned image of the signed Parent Study Approval Form
- An electronic manifest listing of the approved biospecimens, generated by the Parent Study. *The Parent Study will be provided access to their current complete inventory through BioLINCC.*
- Your full or expedited IRB approval for the proposed research

**STEP 3 -** BioLINCC will review your submission for completeness. If complete, they will also link the electronic manifest provided by the Parent Study to the NHLBI Biorepository and generate the BSI Inventory Confirmation Report. This report will confirm that the vials are in inventory and provide vial characterization information to be reviewed by the Parent Study. You will be notified when the BSI Inventory Confirmation Report is ready to download. It is your responsibility to forward the Report to the appropriate Parent Study staff for their review and final sign-off using the sign-off cover sheet to the BSI Inventory Confirmation Report. If there are conflicts between the electronic manifest and the BSI Inventory Confirmation Report (e.g., missing vials, low-volume vials, material type discrepancies, etc.), it is the responsibility of the Parent Study to provide you with a complete replacement electronic manifest and this process will be repeated.

**STEP 4 -** Scan the Parent Study-approved BSI Inventory Confirmation Report sign-off sheet and upload it to your request. BioLINCC will then place the selected vials on hold for you. BioLINCC will also generate and post your Research Material Distribution Agreement (RMDA) and notify you when it is available for you to download, have signed and upload back to your request application.

**STEP 5-** When all requirements have been met, BioLINCC will forward your request for final approval by NHLBI. Upon receipt of NHLBI approval, BioLINCC will release your requisition to the NHLBI Biorepository to initiate the requisition/shipping process.

## 5.0 PREPARATION AND SUBMISSION OF REPOSITORY DATASETS

This section provides information on the preparation of NHLBI Data Repository datasets and associated documentation for submission to BioLINCC in accordance with the NHLBI Policy for Data Sharing. The overall goal of this effort is to produce research datasets and associated documentation which are sufficiently detailed to allow outside researchers to conduct their own analyses while providing protection for the privacy of the participating research subjects. The following sites discuss the rationale and provide methods guidance for NHLBI Data Repository datasets:

General overview of NHLBI Data Sharing Policy:

http://www.nhlbi.nih.gov/funding/datasharing.htm

Guidelines for NHLBI Data Set Preparation:

http://www.nhlbi.nih.gov/funding/setpreparation.htm

FAQs about Sharing Data from NHLBI Studies:

http://www.nhlbi.nih.gov/funding/FAQdatasharing.htm

The repository dataset preparation and submission process essentially involves two steps.

As described below, Step 1 includes the assembly of study data and documents and procurement of institutional certification for the sharing of redacted study data. Step 2 includes the development of a data redaction plan for the creation of shared study datasets. Step 2 also involves the application of the data redaction plan to the study data, and the submission of these redacted data, their associated documentation, and a description of the redactions that were applied.

Parent study coordinating centers which have not previously prepared NHLBI Data Repository dataset packages are strongly encouraged to submit the institutional certification permitting the sharing of study data, key documentation (annotated forms, data dictionaries, documentation for calculated variables), and the draft data redaction plan for BioLINCC and NHLBI review and feedback prior to finalizing the approach. BioLINCC may be contacted for questions and guidance at: http://www.biolincc.nhlbi.nih.gov/contact

**STEP 1: Assembly of materials**

The documentation should be comprehensive and sufficiently clear to enable investigators who are not familiar with a data set to use it. The following types of documents will need to be assembled for electronic submission to NHLBI:

- Study protocol
- Study manuals of procedures
- Informed consent templates
- Data collection forms

- Data coding conventions
- Other materials which provide insight into the study
- Information on the data processing and data quality control procedures that were used
- Dataset documentation and data dictionaries for the final analytic master files (prior to their redaction for sharing).
- Pre-redacted (private) final analytic master files from which the redacted data files will be derived are required for studies funded under NHLBI contract mechanisms or those studies which are also submitting specimens to the NHLBI Biorepository. The submission of pre-redacted final analytic files is optional but preferred for data-only studies funded by grants or cooperative agreements, as they are useful for BioLINCC QA of the redaction process.
- Approval from the institutional IRB for sharing of the study data or language within the informed consent permitting sharing study data with investigators not originally affiliated with the study.

It should be noted that selected study documentation, not including documentation of pre-redacted (private) study datasets but including documentation of data sets to be shared, will be used to describe the study on the BioLINCC website. Examples include Forms, Data Dictionaries, Descriptive Statistics, and the Study Protocol. These documents will need to be accessible to those with disabilities according to section 508 of the Rehabilitation Act. The HHS maintains a website devoted to 508 issues with links to resources on creating and checking accessibility at http://www.hhs.gov/web/508/index.html.

The Parent Study shall provide documentation certifying that the study data were collected in a manner consistent with 45 C.F.R. Part 46 and that the submission of data to the data repository and subsequent sharing for research purposes are not inconsistent with the informed consent of study participants from whom the data were obtained.

**STEP 2 – Redaction of Study Data Sets**

Datasets for sharing should be based upon the final analytic master files and other final supplemental files (as needed) so that the user may approximate published results. However, datasets must be redacted to remove personal identifiers, conform to individual informed consent restrictions, and to recode low-frequency data values if necessary to protect subject privacy. The redaction process may impact the exact replication of published results but is necessary to protect research subjects.

The Parent Study will prepare a plan to redact the study data sets. The redaction plan should be consistent with the techniques and considerations described within the Guidelines for NHLBI Data Set Preparation as provided on the NHLBI website at: http://www.nhlbi.nih.gov/funding/setpreparation.htm.

As specified in the Guidelines, multiple versions of study datasets may be needed if commercial/non-commercial usage restrictions are in effect.

Upon completion of the redaction process, modified study data set documentation which reflects changes made to the included variable types and recodes should be prepared. This documentation will be provided along with the redacted data sets to approved requestors. A summary document which describes the changes and deletions which were applied during redaction should also be included. In addition, a summary documentation file, usually called a README file, should be submitted. This document should provide a complete overview of the data and a description of their use, appropriate for investigators who are not familiar with the data set. It should include a description of significant events which may not be documented in the protocol or other documents that would be useful to understand the submitted data; examples might include addenda describing significant changes in study procedures, cautionary information regarding the interpretation of data elements or which explain apparent inconsistencies in the data or frequently missing data; the abandonment of selected data collections from one or more sites; modifications to questionnaires over time if not documented elsewhere, etc.

The README should also contain a brief description of the study (including a general orientation to the study, its components, and its examination and follow-up timeline), a listing of all files being provided, a description of system requirements, a generation program code for installing a SAS file from the SAS export data file (if appropriate), and a frequency distribution for selected key variables.

Upon completion of the study data set redaction and the preparation of redacted data set documentation, these files will be transferred to BioLINCC. Once transferred, BioLINCC staff will review the submission to verify the transferred records and included variables, re-generate frequencies for comparison to those generated by the study staff, and review data sets for additional items that may need to be redacted or recoded.

## 6.0 SUBMISSION OF BIOREPOSITORY COLLECTION APPLICATIONS

### 6.1 OVERVIEW

The mission of the NHLBI Biologic Specimen Repository (Biorepository) is to acquire, store and distribute quality biospecimens to the wider scientific community using standardized processes and procedures approved by the NHLBI. Submission of a new collection to the Biorepository is by application only, and only applications from collections that can be shared with non-study investigators and are of interest to the wider scientific community will be considered. The application process has three steps: (1) Registration of the clinical study collecting the biospecimens and data (Study); (2) Pre-application to ensure that the collection meets certain essential requirements; and (3) Submission of the required application documents. The required steps are outlined in detail in this Chapter.

**All NHLBI funded multicenter Studies planning to build a biospecimen collection and Studies interested in transferring a collection to the Biorepository must register in BioLINCC.**

For a new Study collection, registration should occur prior to finalizing the plans and procedures to collect the biospecimens. The anticipated study start and completion dates will be recorded in BioLINCC to track the progress of the collection and provide expert assistance, if needed. Registration **does not commit a Study to transfer the collection to the Biorepository once**

**completed, nor does it commit the NHLBI to accept the collection upon completion.** Although BioLINCC and an assigned Biorepository staff can assist a Study as it develops its plans and procedures to collect biospecimens, only completed Study biospecimen collections will be considered for transfer to the NHLBI Biorepository.

*For existing historical collections*, registration should occur ***at least fifteen months*** prior to the anticipated transfer date to provide adequate time to complete the application and review process. There are two review cycles and the timelines for each cycle are provided in Table 6.1. Of note, since not all applications for long term storage in the Biorepository will be accepted, Studies should consider alternative plans for storage.

Review of applications consists of several steps to assess the scientific usefulness of the collection as a shared biospecimen resource. The review groups include the BioLINCC and Biorepository staff, the Study's NHLBI Program Official, the NHLBI Biospecimen Collection Review Panel (BCRP) and the NHLBI Leadership. The BCRP is a trans-extramural NHLBI group that offers recommendations to the NHLBI Program Officials and Division Directors regarding NHLBI biospecimen collections, including acceptance and retention. The BCRP membership includes a Chair from the Division of Extramural Research Activities, and six representatives, with two from each of the Division of Cardiovascular Sciences, the Division of Lung Diseases, and the Division of Blood Diseases and Resources.

The BioLINCC and Biorepository staff review the application for completeness. The NHLBI reviews each collection for potential scientific usefulness, based on the following criteria:

- Utility and limitations of the biospecimens based on the procedures used by the Study to collect, process, label, store and document the collection
- Completeness and quality of the linked Study dataset and Study documents (clinical study and/or laboratory)
- Evidence of potential scientific interest
- Absence of overlap with existing collections in terms of disease and type of collected biospecimens and data

**TABLE 6.1: TIMELINE TO APPLY FOR TRANSFER OF A COLLECTION**
**MINIMUM TIME: 15 MONTHS**

| APPLICATION SUBMISSION – TWO RECEIPT CYCLES | | DUE DATES | |
|---|---|---|---|
| **STEP 1** | Register the Study collection in BioLINCC. | **Apr. 1** | **Oct. 1** |
| **STEP 2** | Pre-application conference call held. Study confirms:<br>1. Biospecimens appropriately consented for sharing with non-study investigators;<br>2. A linked electronic inventory is in use;<br>3. NHLBI Program Official notified; and<br>4. No issues signing the "National Heart, Lung, and Blood Institute's Material Transfer Agreement for Biospecimens" (MTA) | **May 15** | **Nov. 15** |
| **STEP 3** | BioLINCC application form completed and all required documents are submitted | **Jul. 15** | **Jan. 15** |

| INITIAL REVIEW | | COMPLETION DATES | |
|---|---|---|---|
| **Completeness** | BioLINCC and Biorepository resolve missing incomplete documentation | **Aug. 15** | **Feb. 15** |
| **Utility Assessment** | BioLINCC and Biorepository | **Sep. 1** | **Mar. 1** |
| **Potential Scientific Use** | NHLBI Study Program Official | **Sep. 15** | **Mar. 15** |
| **Utility Review** | NHLBI Biorepository Collection Review Panel(BCRP) | **Oct. 31** | **Apr. 30** |
| **Initial Approval** | NHLBI Leadership | **Dec. 31** | **Jun. 30** |

| FINAL REVIEW | | EARLIEST COMPLETION DATES | |
|---|---|---|---|
| **Study Notified** | Written notification of preliminary approval provided. Full Study data set and pilot shipment of biospecimens requested | **Jan. 15** | **Jul. 15** |
| **Full dataset** | Full dataset transferred for review by BioLINCC | **Feb. 1** | **Aug. 1** |
| **Pilot shipment** | MTA signed, and pilot shipment transferred for evaluation by the NHLBI Biorepository | **Feb. 15** | **Aug. 15** |
| **Final Approval** | NHLBI Leadership | **Apr. 15** | **Oct. 15** |

| TRANSFER | | EARLIEST COMPLETION DATES | |
|---|---|---|---|
| **Scheduled** | Finalize transfer logistics | **May 15** | **Nov. 15** |
| **Shipped** | Transfer | **Jun. 15** | **Dec. 15** |

## 6.2 STEPS TO REGISTER A COLLECTION AND TO APPLY TO TRANSFER A COLLECTION

NHLBI Studies engaged in building biospecimen collections should register their Study on the BioLINCC site https://biolincc.NHLBI.nih.gov as early as possible. Table 6.1 provides the timeline and submission due dates to transfer a collection. These dates are set to facilitate the review process and it is the Study's responsibility to complete the steps by the posted dates. Missing a due date may result in the application being reassigned to the next application receipt cycle.

**STEP 1 – REGISTRATION OF THE STUDY COLLECTION:**

To register a Study collection, use the "Biospecimen Collection" link under "Submitting New Collections" on the BioLINCC Home page. Only users with a BioLINCC account may register a collection. An account may be obtained at https://biolincc.NHLBI.nih.gov/register/.

The information collected at registration includes basic identifiers such as the Study name and acronym, and contact information for the Principal Investigator, principal study contact, and NHLBI Program Official. The registration form also collects:

- Information on the current status of the study (in planning, in process or completed) and the actual or anticipated study collection start and end dates
- Basic information on the study itself, such as a brief summary of the protocol, the number of participating centers, the use of central data management and/or specimen processing labs, the target/actual accrual, and the anticipated number of study biospecimen collection visits per participant

A call may be requested at any time to discuss the BioLINCC and Biorepository programs and the resources which may be available to the Study.

**STEP 2 – PRE-APPLICATION CONFERENCE CALL:**

The pre-application call is to confirm that a Study collection meet the following essential requirements prior to the Study submitting an application to transfer the collection to the Biorepository. Applications will not be accepted if these requirements cannot be met.

1. Biospecimens in the collection must be appropriately consented for use by non-study investigators
2. The study must possess an electronic biospecimen inventory that can be linked to the Study data at a sample and visit level
3. The transfer must have been discussed with an NHLBI Program Official
4. The Study must confirm that the "National Heart, Lung, and Blood Institute's Material Transfer Agreement for Biospecimens" has been reviewed and can be signed by the appropriate Study investigator(s) and an Authorized Institutional Official.

The pre-application Step is initiated by the Study by sending a request to hold a pre-application conference call through the BioLINCC website. The request should include the contact information for the required Study participants identified below. BioLINCC will arrange the call using this information. Participants on the call should include:

- Study investigator(s)/coordinator(s) responsible for designing, implementing and maintaining the collection
- Study NHLBI Program Official
- NHLBI BioLINCC/Biorepository COR(s)
- NHLBI BioLINCC and Biorepository staff

BioLINCC will distribute the conference call agenda prior to the call and will include the items listed below. BioLINCC will prepare minutes from the call and provide a draft to all participants for review.

1. Status of the Study's biorepository collection
2. Review of the pre-application and application process and timeline to transfer the collection to the Biorepository
3. Action Items and Next Steps

Studies confirming that they can meet the essential requirements described above will be asked to document that this is the case. Studies which indicate that they will be unable to meet the essential requirements will not be considered further for inclusion in the NHLBI Biorepository. This action will be documented in the call minutes.

**STEP 3 – APPLICATION SUBMISSION:**

Following successful completion of the pre-application process (Step 2), the Study will be given access to the Collection Application screen on the BioLINCC website.

The information gathered online on the Collection Application screen is as follows:

- Scientific importance.
    - The applicant must describe the scientific importance of the proposed Study collection and address why the collection would be a valuable addition to the Biorepository. The application should also provide the number of ancillary studies using the biospecimens and a list of the ancillary study publications. If no ancillary studies have been conducted, the applicant should provide an explanation of why this is the case.
- Wider Interest.
    - The applicant must provide evidence of interest by the non-Study community in using the collection and describe potential research areas.
- Number of Study centers that collected the biospecimens.
- Information on:
    - Number of collection centers

    - Type of processing facilities
    - Use of a data center
    - Average number of Study visits with biospecimens
    - Availability of standard procedures to collect, process and store biospecimens and data
- QA procedures description
- Availability of funding to transfer the collection

Study staff will be asked to upload the required documents and data file(s) to the appropriate section on the "Checklist" Tab within their Request page by the application submission due date (see Table 6.1). The information to be uploaded includes summary documents prepared by the Study for the submission application and the documents which were used to manage the Study. This activity will be coordinated by BioLINCC staff. The Study is encouraged to request technical assistance in the upload process via the BioLINCC website, if needed.

The required summary documents are as follows. These documents will be used to facilitate the application review by BioLINCC, the Biorepository and NHLBI:

- An index of the submitted Study documents that identifies the uploaded document file name, and specific associated page number(s), for the following key elements:
    - Study protocol
    - The data collection/data management procedures which were used, including the procedures to ensure data integrity and to link the Study data to the biospecimen inventory
    - The procedures used to collect, process, label, track, store, and ship biospecimens
    - The QA/QC processes that were implemented to validate and monitor the biospecimen procedures
    - Information on laboratory assays performed on fresh and frozen biospecimens
- A summary of the informed consent documents used at the collection sites to collect the biospecimens with information on:
    - restrictions for biospecimen use by non-Study investigators
    - changes to the restrictions for biospecimen use over time, including the effective date

The required Study documents and files for the initial assessment of the biospecimen collection are:

- The final version of the Study protocol

- The document(s) used to manage the Study (e.g. Manual of Procedures, Laboratory Procedures, Data Management Handbook, etc.) that describe the key elements identified in the index document.
- The annotated Study data forms and worksheets,
- Study data dictionary describing the data variables
- The IRB approved Informed Consent Document from each collection site that was in use at the completion of the Study
- A structured data file (e.g., SAS, Excel or other common database format) with a subset of the data collected that includes a complete listing of all the biospecimens in the proposed transfer inventory. For each biospecimen vial/sample, the following variables should be included-- data elements which are not available should be left blank:
  - Study subject ID
  - Gender
  - Race
  - Study visit identifier
  - Informed consent data as they relate to the specific specimen, including any usage restrictions if a layered (tiered) consent was used
  - Date/time of specimen collection
  - Storage temperature between collection and processing
  - Date/time processing initiated
  - Biospecimen vial/specimen ID
  - Material type
  - Tube type and/or preservative used
  - Volume or quantity
  - Date/time frozen
  - Vial comments *(e.g., sample condition, indications of hemolysis, etc.)*
  - Storage temperature
  - Stored vial location

## 6.3 REVIEWING APPLICATION DOCUMENTATION

### 6.3.1 OVERVIEW

The review of an application includes an initial assessment of the collection's utility based on the application documents, and a final review of the collection's utility based upon the findings from the biospecimen pilot shipment and review of the full dataset.

**THE INITIAL ASSESSMENT INCLUDES THE FOLLOWING THREE ONLINE REVIEWS USING THE INFORMATION PROVIDED IN THE APPLICATION.**

1. BioLINCC and Biorepository staff will assess the utility and limitations of the biospecimens based on these criteria:

    a. The procedures used by the Study to collect, process, label, store and document the collection.

    b. The completeness and quality of the linked Study data (clinical study and/or laboratory).

2. The Study NHLBI Program Official will assess the potential scientific use of the collection and potential scientific interest in the collection.

3. The BCRP will assess the overall utility of the collection.

    A report will be prepared by the assessor(s) for each of these reviews. The BCRP report will provide recommendations to the NHLBI Leadership on whether the application should or should not be considered for acceptance. The NHLBI Leadership will review the application taking into consideration the results of the reviews conducted by the BioLINCC and Biorepository staff, the Study NHLBI Program Official, and the BCRP.

    Studies that have a favorable review from the NHLBI Leadership will be requested by BioLINCC to 1) send a pilot shipment of their specimens to the Biorepository; and 2) send their Study datasets to BioLINCC. The Biorepository will assess the physical integrity of the specimens in the pilot shipment and report findings to the NHLBI. Similarly, BioLINCC will assess the completeness and quality of the Study data and accompanying documentation. If no issues related to the biospecimens or data are noted, the transfer will proceed. If issues are identified, then the BCRP Chair will be notified and a plan to resolve the issues will be developed. Issues adversely impacting the integrity of the collection may result in the application to transfer the collection being denied.

### 6.3.2 BIOREPOSITORY AND BIOLINCC ASSESSMENT

The Biorepository technical staff will prepare a report to describe the technical aspects and limitations of the proposed Biorepository collection. The report will include the following descriptive information:

- Utility and limitations of the biospecimens based on the procedures used by the Study to collect, process, label, store, and document the collection. The report will include comments on the types of research that may or may not be possible, based upon specimen processing and storage methods, such as additives, preservatives, and pre-draw patient preparation and other considerations.
- Estimate of funds needed to transfer and/or re-label samples.
- Potential overlap with stored Biorepository collections.

BioLINCC staff will prepare a report to describe technical aspects and potential limitations of the proposed collection based upon the structured data file which is uploaded to the application:

- ability to link vials as described within the structured data file to the subject and visit data in the clinical data set
- descriptive tabulations of the number of subjects with biospecimens available at all visits, and the number of vials at each time point
- tabulations of the numbers of vials, by material types and visit, within the proposed transfer
- descriptive tabulations of biospecimen availability by consent restrictions
- description of the types of data submitted, and an assessment of data quality, integrity, consistency and completeness

### 6.3.3 NHLBI PROGRAM OFFICIAL ASSESSMENT

Following the review of the application documents by BioLINCC and Biorepository staff, the Study NHLBI Program Official sponsoring the application will prepare an assessment of the scientific usefulness of the biospecimens. The assessment will include a review of the uniqueness of the collection and the potential use of, and interest in, the collection by the scientific community. Any limitation to the scientific use of the biospecimens noted in the Biorepository review will be taken into consideration. The assessment will be added to the Study documents in BioLINCC.

### 6.3.4 NHLBI BIOREPOSITORY COLLECTION REVIEW PANEL (BCRP) ASSESSMENT

Following the NHLBI Program Official review, the BCRP will perform an online review of the Study materials and the assessment reports. Access to these materials will be provided two weeks prior to the BCRP face-to-face meeting. Each application will be discussed at the meeting and the BCRP Executive Secretary will prepare recommendations regarding acceptability of the collection.

### 6.3.5 NHLBI LEADERSHIP REVIEW

The Study application, assessment reports, and BCRP recommendations will be provided to the NHLBI leadership for discussion at a face-to-face meeting. The results of the discussion will be conveyed to the BCRP Chair for distribution to the BioLINCC and Biorepository COR(s). Studies will be notified of the outcome of the review through BioLINCC.

Applications considered acceptable based on the materials submitted in the application will be given a preliminary approval. These applications will undergo a final review to assess the physical integrity of the biospecimens and completeness of the study data to confirm the assessed utility of the collection.

## 6.4 REVIEWING INTEGRITY OF THE BIOSPECIMENS AND DATA

### 6.4.1 OVERVIEW

Studies receiving preliminary approval will be asked to submit the following:

1. A pilot shipment of biospecimens to the Biorepository to allow for assessment of the physical integrity of the specimens
2. The complete Study documentation and data, including the final inventory and linking file(s)

The Biorepository and BioLINCC staff will prepare assessments of the final materials for review by the NHLBI. Issues impacting the utility of the collection will be noted and possible resolutions provided. Issues that cannot be resolved may result in the withdrawal of the initial approval to transfer the collection to the Biorepository.

### 6.4.2 PILOT SHIPMENT

Prior to arranging a pilot shipment, an approved Material Transfer Agreement (MTA) will be required. Studies funded by an NHLBI contract will follow the contract requirements for specimen transfer.

The MTA will be generated by the BioLINCC website using information already provided in the application documents. The applicant will be instructed to download the MTA, obtain the appropriate signatures and upload the signed MTA to their application page in BioLINCC. Materials cannot be transferred to the NHLBI Repository until the MTA has been signed by the appropriate Study signatories and NHLBI staff, and posted in the Study application on BioLINCC.

Studies funded by an NHLBI contract will follow the contract requirements for specimen transfer.

Following completion of the MTA/contract requirement, the Study will be informed through BioLINCC of the steps to arrange a pilot shipment of biospecimens. Typically, the facility holding the Study collection will send a request to the Biorepository via email and a Biorepository staff member will be in contact with the facility to provide guidance on arranging the shipment. The Biorepository can provide shippers and shipping protocols, if requested. Shipping expenses will be paid by the Study.

The pilot shipment must include an electronic shipping manifest. Study staff will be responsible for completing the electronic manifest for all samples in the pilot shipment and submitting the file electronically at the time of shipment. Biorepository staff will assess the shipment by comparing the data elements listed on the shipping manifest to the information on the vial labels and characteristics that can be observed (i.e., material type, hemolysis, volume). A report will be provided to the NHLBI and will include discrepancies and recommended corrective actions. Discrepancies will require correction prior to transfer of the full collection. The number and type of discrepancies will be reviewed by the NHLBI to determine if the number and type of discrepancies makes the collection unacceptable.

### 6.4.3 TRANSFER OF THE FULL CLINICAL DATA SET

BioLINCC will provide a secure site for the transfer of Study data and associated documentation. Study data will be converted to SAS format. BioLINCC staff will review the materials provided, and will ensure that the subject ID, race, gender, consent (if applicable), and visit (if applicable) can be linked to biospecimen data found in the manifest. Any Studies that have a tiered consent should have a variable in the data that details which level of consent the subject gave. No biospecimens should be included in the manifest that cannot be linked to data, and no biospecimens should be included in the manifest for subjects who did not agree to make their specimens available for wider use.

Studies that have multiple datasets will be also assessed on their ability to be linked to one another. BioLINCC will also examine variables contained in multiple datasets, such as subject ID and visit, to ensure that they have been formatted consistently across all datasets.

All documentation should be provided in its original electronic (not scanned) state. Documentation describing the data will be reviewed for completeness. The data documentation should include the following:

- a description of each of the variables
- a formats file or codebook that provides details of how variables were coded
- all versions of case report forms used to collect the data
- a document that describes any modifications (e.g. redactions or recodes) to the data

BioLINCC will provide a report that summarizes an assessment of the quality of the data and the ability to link the data to biospecimens.

### 6.4.4 REVIEW AND SIGNOFF

Approval to transfer the collection will be made following the successful completion of the pilot shipment and the data transfer. Studies will be asked to work with the Biorepository to finalize the transfer details.

Issues identified from the collection and data assessments will be discussed with the BCRP Chair and Study NHLBI Program Official. Issues that cannot be resolved with the Study may result in the withdrawal of the initial approval to transfer the collection to the NHLBI Biorepository.

## 6.5 TRANSFER OF THE COLLECTION

The facility storing the Study collection will receive a request via BioLINCC to initiate discussion to finalize the arrangements to transfer the collection. Typically, a conference call with Study staff to discuss the details will be arranged. Biorepository staff member will provide guidance on packing, shipping and logistics.

Upon receipt, a subset of the collection will undergo the same inspection and reporting process as described for the pilot shipment (Section 6.4.2). The Study site and data management center must be able to provide corrective actions for any discrepancies found during the inspection process.