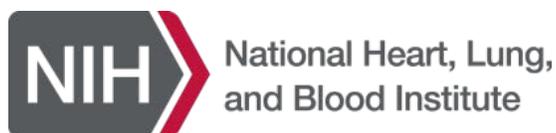




# The BioLINCC Handbook

Guide to Accessing the NHLBI Biologic  
Specimen and Data Repositories

<https://biolincc.nhlbi.nih.gov>



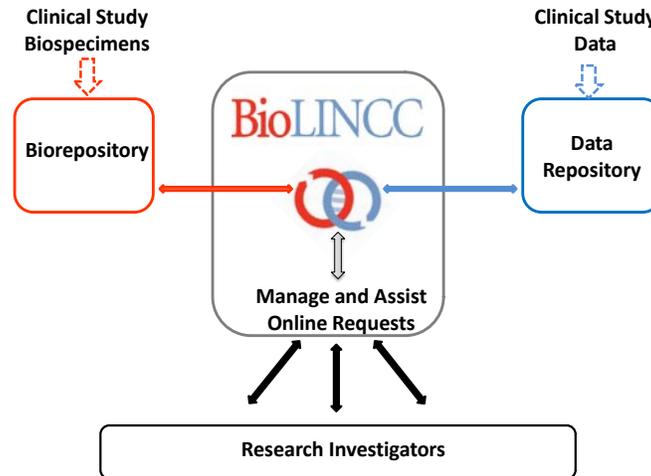
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1.0 BIOLOGIC SPECIMEN AND DATA REPOSITORIES INFORMATION COORDINATING CENTER  
1.1 OVERVIEW

Figure 1.1: Facilitating Access to NHLBI Biospecimens and Data



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 “to 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, which has been 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 <https://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, additives, 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 <https://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 580,000 participants from over 110 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, per redaction plans consistent with NHLBI policies. 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 <https://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 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

The screenshot shows the BioLINCC home page layout. On the left is a vertical 'Main Menu' (2.2.1) with categories like 'Open Studies', 'Non-BioLINCC Resources', and 'About BioLINCC'. At the top right is a 'Full Website Search' box (2.2.4). Below the header is a 'Welcome!' message and a 'Log In or Register' link (2.2.2). The main content area features a 'Search for Study Datasets and/or Biospecimens' section (2.2.3) with a search form and filter options. On the right is a 'Recent News' section (2.2.5) listing new studies.

### 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 **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**.

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

The third section provides information and links to **Funding Opportunities** which may be applicable to research using NHLBI Biorepository or Data Repository resources.

The fourth 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 fifth section within the main menu, **About BioLINCC**, includes links to the **BioLINCC Handbook, Forms and Templates** used during request processes, **FAQs**, and a **Glossary** of terms used in BioLINCC documents.

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

There is an eighth 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 through the log-in webpage.

Once logged in as a registered user, an eighth 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 <https://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**

This chapter reviews the process to request biospecimens and data in the Parent Study's Open Period, which is when the Study biospecimens and data can be shared through the BioLINCC website (see NHLBI Data Set Sharing Policy timeline at <http://www.nhlbi.nih.gov/funding/datasharing.htm>.) Investigators wishing to access biospecimens and data prior to the Open Period, i.e., when the biospecimens and data are in the Parent Study's Proprietary Period, should contact the Parent Study directly.

The BioLINCC website at <https://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.  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 <https://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 and are not interchangeable.

**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 are transferred to the requestor as secure transfers through the website. 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-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 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**

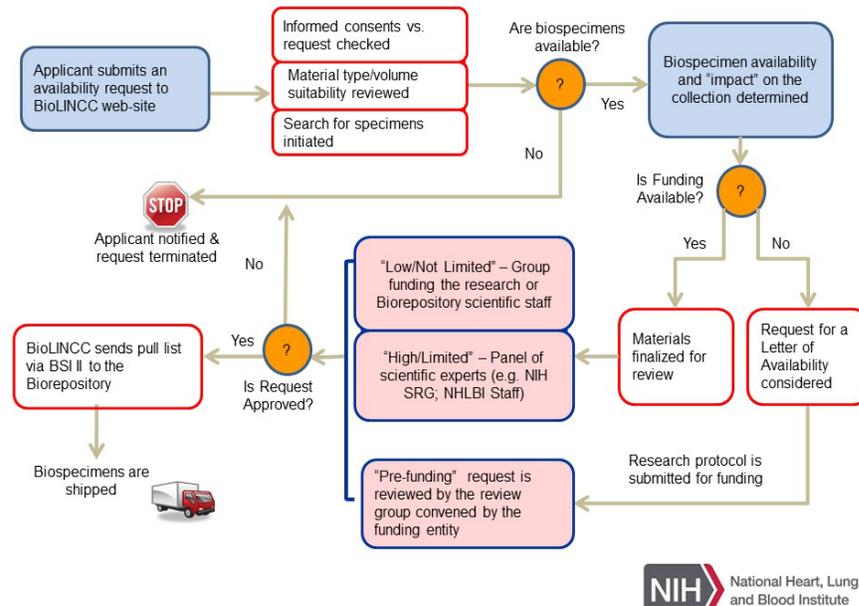
For biospecimen requests, the review takes the following guidelines into consideration:

- 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 unfrozen specimens if previously frozen 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 “COLLECTION 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. Restrictions vary by collection. For example, the consent may restrict the research to a specific disease area or for non-commercial research. 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 the impact of the request, if fulfilled, on the collection. The impact on the collection is assigned using two categories: “low impact” and “high impact”. The elements taken into consideration in determining “impact” include historical use of the collection, the material type, volume remaining, potential for generating additional aliquots or 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”: Definitions and Review Options**

Impact on the Collection	Definition	Review Options
Low Impact	Not a limited resource <i>After current request fulfillment, 4 or additional new requests can be supported based upon historic use (e.g., volume/quantity)</i>	Funding group of Biorepository scientific expert review. NHLBI staff will be consulted if questions regarding the scientific use of the biospecimens arise.  For biospecimens that are considered abundant and not unique, no request limit will be imposed.
High Impact	Unique and limited resource <i>After current request fulfillment, 3 or fewer additional new requests could be supported based upon historic use (e.g., volume/quantity)</i>	A panel of scientific experts (e.g., NIH SRG or NHLBI Extramural staff with expertise the scientific area).  NHLBI staff will be consulted when the last aliquot from a collection time point is requested.

### 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 will request that the Biorepository prepare and ship the requested biospecimens.

## **3.4 REVIEWING REQUESTS FOR DATA SETS**

### **3.4.1 OVERVIEW**

All reviews for data in the Open Period are coordinated by BioLINCC and are performed by the NHLBI 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.

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.

### **4.0 APPLYING FOR BIOSPECIMENS 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. 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 DATA REPOSITORY DATASETS AND DOCUMENTATION**

### **5.1 OVERVIEW**

This Chapter 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/research/funding/human-subjects/set-preparation-guidelines.htm>

FAQs about Sharing Data from NHLBI Studies:

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

OF NOTE: For Studies applying to transfer a biospecimen collection to the NHLBI Biologic Specimen Repository (Biorepository), the application is not considered complete until all the datasets and documents described in STEP 1 are submitted to BioLINCC (see Chapter 6 for the application process).

## 5.2 PREPARATION AND SUBMISSION

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

As described below, Step 1 includes the assembly of study data and documents and the 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 and the application of that plan to the study data. Step 3 includes 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: <https://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. Whenever possible, documents should be in their original electronic state, rather than scans of hard copies:

- Summary with the Study objectives, background, subjects, and conclusions
- Study protocol
- Study manuals of procedures
- Primary manuscript
- Informed consent template(s)
- Annotated data collection forms
- Data coding conventions
- Other materials which provide insight into the study to assist use by non-Study investigators, such special adjudication panels or algorithms to calculate outcome variables

- Information on the data processing and data quality control procedures that were used
- 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.
- 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 in the following circumstances:**
  - Studies which are also submitting specimens to the NHLBI Biorepository
  - Studies funded under NHLBI contract mechanisms

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.

- For Studies applying to transfer a biospecimen collection to the NHLBI Biorepository the following additional data files are required:
  - A complete inventory file of the specimens to be transferred, including all relevant data elements regarding vial identifiers, specimen collection parameters, material type, additive/preservative/storage information and other by-vial data as maintained in the Study's biospecimen inventory tracking system.
  - A linking file which clearly associates each biospecimen with their clinical and/or laboratory data.

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 DHHS 45 C.F.R. Part 46, Protection of Human Subjects, 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 final analysis level files from all study visits, laboratory measurements, study procedures, and outcome elements along with other final supplemental files (for example, required calculated variables) so that users may approximate published results and conduct new secondary analyses. Datasets must be redacted to remove personal identifiers and data collected solely for administrative purposes, and must conform to individual informed consent restrictions. In addition recodes of selected low-frequency data values may be necessary to protect subject privacy and minimize re-identification risks. 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/research/funding/human-subjects/set-preparation-guidelines.htm>

If commercial/non-commercial usage restrictions are in effect, multiple versions of study datasets may be needed, or alternatively, an informed consent file supplied specifying the consent level for each participant (unrestricted, non-commercial use only) such that data subsets can be created by BioLINCC.

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.

### **STEP 3 – TRANSFER AND BIOLINCC REVIEW OF REDACTED DATA SETS AND DOCUMENTATION**

Upon completion of the study data set redaction and the preparation of redacted data set documentation, these files will be ready for transfer. At this point, the Study should contact the NHLBI Data Repository Program Director, Sean Coady, at [coadys@nhlbi.nih.gov](mailto:coadys@nhlbi.nih.gov).

Once transferred, BioLINCC staff will review the submission to verify the transferred records and included study data 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. 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.

#### **5.3 STUDY DATA FOR A PROPOSED BIOSPECIMEN TRANSFER**

Study data associated with biospecimens proposed for transfer to the NHLBI Biorepository will follow the same procedure and documentation requirements as described in Section 5.2, above. As noted in Step 1, Assembly of Materials, a complete inventory file of the specimens to be transferred and a data file which clearly links each biospecimen with their clinical and/or laboratory data must be included in the data submission. Biospecimens that cannot be linked to data or which were collected from subjects who did not agree to make their specimens available for wider use should not be included in the inventory data files submitted, nor should they be sent to the NHLBI Biorepository if the application is approved.

In addition to the review processes described in Section 5.2, BioLINCC staff will review the materials provided to ensure that the subject ID, race, gender, consent (if applicable), and visit (if applicable) can be linked to biospecimen data found in the associated inventory as part of the application to transfer the biospecimen collection (see Chapter 6). Any Studies that have a tiered consent should have a variable in the data that details which level of consent the subject gave.

BioLINCC will prepare a report that summarizes an assessment of the quality of the data and the ability to link the data to biospecimens. This report will be included in the materials provided to the NHLBI during the biospecimen application review process.

#### **6.0 PREPARATION AND TRANSFER OF AN NHLBI FUNDED BIOSPECIMEN COLLECTION TO THE NHLBI BIOREPOSITORY**

##### **6.1 OVERVIEW**

This Chapter provides information on transferring the [custodianship](#) of an NHLBI funded quality biospecimen collection to the NHLBI, including relocating the biospecimens and the clinical study (Study) data to the NHLBI's Biorepository and Data Repository. The NHLBI becomes the caretaker of the collection and assumes responsibility for maintaining the collection. Custodianship also includes the rights to determine conditions under which the biospecimens are accessed, used,

and retained. The benefits of transferring custodianship to the NHLBI are presented in a [video](#) and include 1) long term storage in an established facility, at no cost to the Study; 2) biospecimens are inventoried and tracked in a secure centralized database and made available online through the BioLINCC website; 3) all requests undergo a scientific and technical review; 4) the original Study is acknowledged in publications.

Only quality biospecimen collections from funded NHLBI clinical studies with potential scientific utility and that can meet the following four requirements will be considered for transfer to the Biorepository.

- (1) An Institutional Review Board has reviewed and verified that submission of the collection to the Biorepository for subsequent sharing with non-Study investigators for research purposes is consistent with the informed consent of Study participants.
- (2) A data file in SAS or Excel/CSV format can be provided electronically of the current biospecimen inventory. This file should include the variables described in Section H Q5 of the Incoming Biospecimen Collection Questionnaire at [https://biolincc.nhlbi.nih.gov/website\\_forms/](https://biolincc.nhlbi.nih.gov/website_forms/) and should be included in the initial collection application.
- (3) The Parent Study PI(s) will sign the NHLBI Material Transfer Agreement (MTA) for Biospecimens prior to shipment of vials/samples to the NHLBI Biorepository.
- (4) The Parent Study acknowledges that biospecimen collections in the NHLBI Biorepository are subject to periodic utilization assessments and possible reduction.

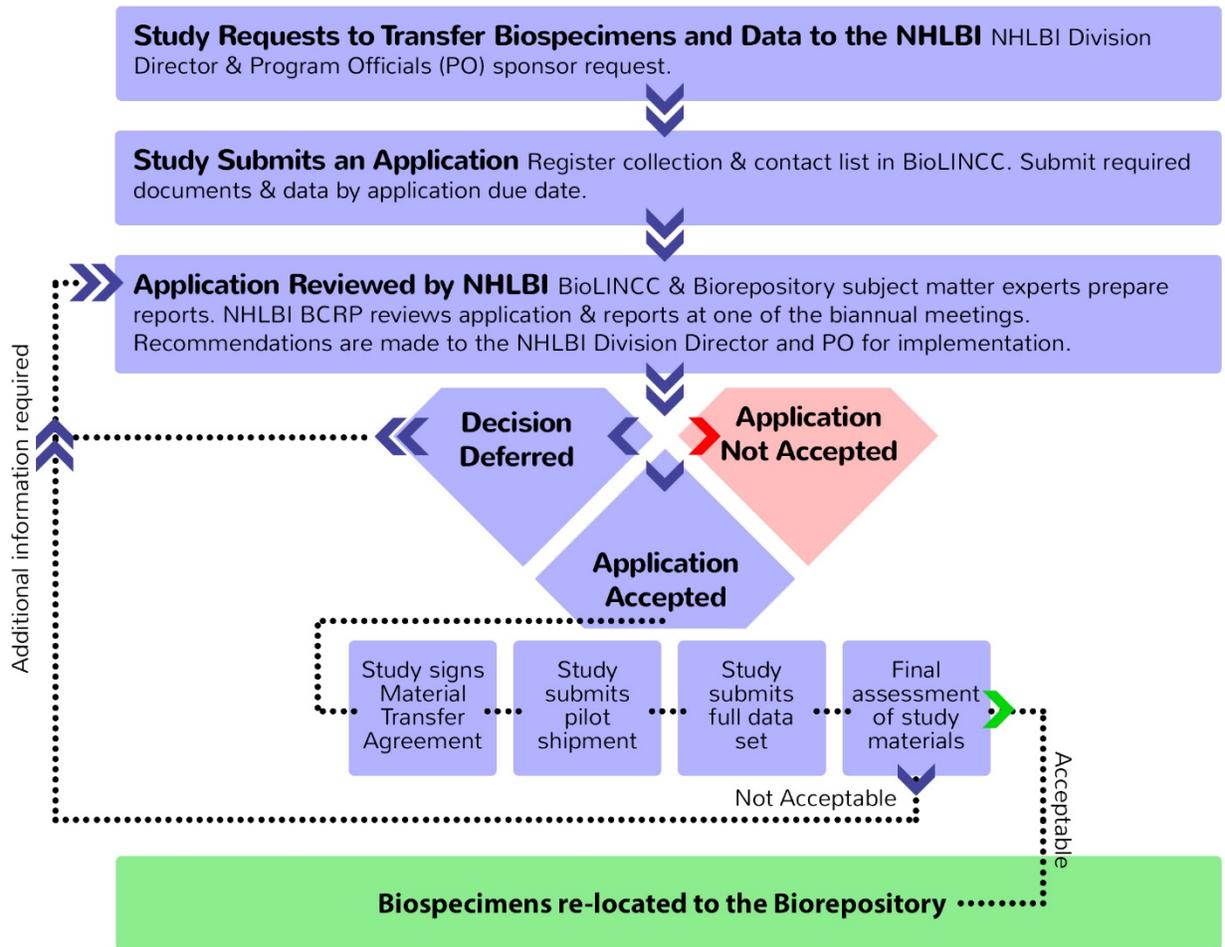
All biospecimen and data collections undergo an assessment for potential scientific utility and quality prior to acceptance into the Biorepository. The quality of a Study collection is based on the completeness of the collection and on the procedures used by the Study to ensure the quality of the biospecimens and data. It is recognized that building a quality biospecimen collection suitable for Study and/or future use by the broader research community requires considerable planning and careful and deliberate practices, as well as adequate resources to build, store and sustain a collection when the Study's primary funding ends. The NHLBI Biorepository Guide to Building Biospecimen Collections for Study and Future Research Use is available at [https://biolincc.nhlbi.nih.gov/nhlbi\\_biorepository\\_guide/](https://biolincc.nhlbi.nih.gov/nhlbi_biorepository_guide/) to assist Studies with this effort. It is recommended that Studies use this document and the [NHLBI Biospecimen Collection Questionnaire](#) to build, monitor and curate their collections.

The assessment for scientific utility is performed by the NHLBI Biospecimen Collection Review Panel (BCRP). The BCRP membership includes a Chair and two representatives from each NHLBI Extramural Division: the Division of Cardiovascular Sciences, the Division of Lung Diseases and the Division of Blood Diseases and Resources. The BCRP meets two times each year to review applications to transfer the biospecimens to the Biorepository to serve as an "open" scientific resource through the BioLINCC website. The review is based on information provided by the Study in the Questionnaire and in the reports prepared by BioLINCC and Biorepository contract staff with expertise in data management, statistical programming, biorepository management

and biospecimen collection, processing, labelling and analysis. These staff members serve as subject matter experts and provide assessments throughout the transfer process regarding the quality and completeness of the biospecimens and data. BCRP recommendations regarding the suitability of the collection as an “open” scientific resource through the BioLINCC website are sent to the Director of the NHLBI Division funding the Study for acceptance and implementation. Not all requests to maintain a collection in the Biorepository are approved and Studies should have an alternate plan(s) in place.

Figure 6.1 provides a diagram of the key elements of the transfer process. A Study should contact their NHLBI Program Officer (PO) at least 18 months before the proposed transfer date to discuss the process and a transfer timeline. Of note, the biospecimen collection cannot be transferred until the data have been received and reviewed by BioLINCC. It is important that Studies take this into consideration when developing their timeline. Missing and/or incomplete data and information will result in delays and could result in a collection not being accepted.

**Figure 6.1: Preparation and Transfer Process**



## 6.2 REQUESTING TO TRANSFER BIOSPECIMENS TO THE NHLBI BIOREPOSITORY

Preparing to transition a collection from Study use to an “open” scientific resource requires considerable planning to curate the Study documents and data, assess the scientific utility of the collection and complete all the activities necessary to transfer the biospecimens. In the experience of the BioLINCC and Biorepository programs it takes a minimum of 18 months to successfully accomplish this. Study Principal Investigators (PIs) and/or the NHLBI Program Officials (POs) responsible for Study oversight should, therefore, initiate discussions regarding the transfer of the custodianship of the collection to the NHLBI and the relocation of the biospecimens and data to the NHLBI’s Biorepository and Data Repository at least 18 months prior to the anticipated transfer date.

Requests to transfer custodianship and relocate the biospecimens are made by the Study’s NHLBI PO(s) to their Division Director. The NHLBI PO(s) will discuss the Study’s interest in transferring the biospecimens and data with the Director of the Division funding the Study. If the Division Director supports the transfer, the NHLBI PO (s) will then discuss the request with the Division

BCRP representatives and NHLBI BioLINCC Contracting Officer Representative (COR) and/or NHLBI Biorepository COR to review the process, set the transfer timeline and review the NHLBI resources which will be needed to acquire the biospecimens and data.

To be eligible for this resource program, the Study has to demonstrate that the collection is of interest to the scientific community, that it has been collected in a rigorous and well documented manner, that biospecimens can be shared with non-Study investigators, that the Study data can be linked to the appropriate vials in the collection, that an electronic inventory with the location of each vial is available, and that the Study will sign a Material Transfer Agreement (MTA). Requestors should be aware that biospecimens cannot be transferred to the Biorepository until the Study data have been submitted to, and accepted by, the Data Repository. In addition, the collection will be “open” immediately following a QC of the biospecimen inventory. Storage of collections for Study investigator use only is not provided.

### **6.3 SUBMITTING AN APPLICATION TO TRANSFER BIOSPECIMENS TO THE NHLBI BIOREPOSITORY**

All applications to transfer a collection to the Biorepository undergo a rigorous assessment for potential scientific utility and biospecimen quality. The reviews assess the completeness and quality of the Study data and documentation, the ability to link each sample to its Study data, the integrity of the biospecimens based on the Study procedures and the collection’s potential scientific future use.

Applications are reviewed by the NHLBI BCRP two times a year at scheduled meetings. The application submission dates are available at [https://biolincc.nhlbi.nih.gov/submit\\_biospecimens\\_and\\_datasets/](https://biolincc.nhlbi.nih.gov/submit_biospecimens_and_datasets/). Given that unanticipated delays frequently occur, applications should be submitted at least 18 months before the proposed transfer date. The time to complete the assessment depends on the ability of the Study to submit the required documents and to respond promptly to review questions.

#### **6.3.1 REGISTERING THE STUDY TO INITIATE THE APPLICATION**

The assessment is initiated by registering the Study on the BioLINCC website following approval by the NHLBI (see Section 6.2).

The information collected at registration includes basic identifiers such as the Study name and acronym, and contact information for the Study PI(s) and NHLBI PO(s). A list of Study contacts who are key to the transfer of data and the biospecimens must be provided. The NHLBI PO(s), the Study PI(s) listed on the registration form and the additional contacts **MUST** be registered as BioLINCC website users to ensure they receive correspondence regarding the application. BioLINCC website user accounts are free and may be obtained at <https://biolincc.NHLBI.nih.gov/register/>.

Upon request, BioLINCC will schedule a call to review the registration and application process.

### 6.3.2 SUBMITTING THE APPLICATION DOCUMENTS

Following registration, the required information must be uploaded to the registration page. These materials are essential to completing the initial scientific and technical review of the biospecimens and data, and incomplete submissions will not be sent to the BCRP for review. Studies will be informed of the status of their submission through their BioLINCC website account.

The required application documents and files include:

- The NHLBI Biospecimen Collection Questionnaire. This document includes detailed information regarding the scientific value and technical quality of the collection.
- A SAS or Excel/CSV data file and data dictionary that includes the variables listed in Questionnaire, Section H #5. The data file should be structured to list one observation for each individual biospecimen sample in the inventory and include all the samples that the Study proposes to send. The data dictionary should include a description of the variables and their formats. For variables that are not captured electronically, the data dictionary should indicate if this information is captured non-electronically and, if it is, where and what data are captured.
- Study protocol (most current version).
- Study informed consent template.
- A summary of the informed consent documents used at the collection sites to collect the biospecimens with information on:
  - restrictions on biospecimen use by non-Study investigators
  - restrictions on biospecimen use by research topic (e.g., disease or organ-specific), genetic use restrictions, commercial entities, etc., if applicable
  - changes to the restrictions for biospecimen use over time, including the effective date (s)
  - site specific changes to the Study informed consent related to biospecimens and data use
- The Study document(s) with the procedures used to:
  - collect, process, label, aliquot, track, store, and ship each biospecimen type
  - validate and monitor the biospecimen collection throughout the Study
  - perform the laboratory assays performed on fresh and frozen biospecimens
- The names and contact information for Study staff (data coordinating center and laboratory) essential to the maintenance of the collection.

### 6.4 REVIEWING THE APPLICATION TO ASSESS THE SCIENTIFIC UTILITY AND TECHNICAL QUALITY OF THE BIOSPECIMEN COLLECTION

The BCRP meets two times a year to review applications. Prior to the review, reports are prepared by the Biorepository and by BioLINCC as described below. During the report preparation process, questions related to incomplete submission of required Study application

documents and files, difficulties encountered when trying to find required information, and concerns about the utility of the collection for future sharing, etc., will be sent to the Study through their BioLINCC website account. The NHLBI PO(s) will be included in all correspondence. Delays in responding to questions or incomplete submissions may delay the BCRP review to the next scheduled meeting.

Using the information submitted through the BioLINCC website, the Biorepository subject matter experts prepare a report describing the technical quality and possible limitations of the collection. The report includes information on:

- The potential utility and limitations of the biospecimens based on the procedures used by the Study to collect, process, label, store, and document the collection.
- 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.
- An estimate of funds needed to transfer, consolidate and/or re-label samples.
- The potential overlap with stored Biorepository collections.

A separate report is provided by the BioLINCC subject matter experts on the submitted data files. This report includes information on:

- The ability to associate vials in the specimen inventory with subject and visit data.
- 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.
- Tabulation of the number of sample boxes and number of vials within the boxes to assess freezer requirements and the potential need to consolidate the collection.

The PO(s) sponsoring the Study request attends the BCRP meeting to discuss the request and address questions related to the utility and size of the collection. Based on the information provided and the meeting discussion, the BCRP makes its recommendations to the NHLBI Director of the Division sponsoring the application. The overall recommendation may be to 1) accept the application to transfer the biospecimens, or 2) ask the Study to provide additional information to address questions for the next BCRP meeting, or 3) deny the application to transfer the biospecimens. Additional recommendations from the BCRP may include suggestions regarding size of the inventory transfer (i.e., the entire collection vs. a subset). The overall BCRP recommendation and specific suggestions are compiled for review by the Division Director, who decides whether to proceed with the application process, defer it pending additional information or deny the application.

The Division Director's decision is forwarded to the Study PI(s) and additional contacts through the BioLINCC account.

## **6.5 TRANSFERRING A COLLECTION TO THE NHLBI BIOREPOSITORY**

Studies with applications that have undergone the scientific assessment by the BCRP and are accepted for transfer to the NHLBI Biorepository will work with the BioLINCC and Biorepository programs to establish a timeline to complete the transfer process. The process includes signing the [NHLBI Material Transfer Agreement \(MTA\)](#), submitting a pilot shipment of biospecimens to assess the physical condition of the vials and labels, and submitting the full Study data and documentation.

Questions that arise during the transfer process that impact the scientific utility of the collection are sent to the Study through the BioLINCC account and these must be addressed by the Study prior to relocating biospecimens to the Biorepository. Incomplete responses to these questions may result in a re-review of the application by the BCRP. The types of questions include questions related to the quality and/or completeness of the biospecimens, data or documentation.

### **6.5.1 INITIATING THE TRANSFER**

BioLINCC will schedule a call using the contact list provided at registration to review the process and establish a timeline with milestones. Study participants on the call must include the NHLBI PO(s), the Study PI(s), and the Study members responsible for preparing the data sets and the pilot shipment of biospecimens. BioLINCC will prepare action items which include the timeline and milestones agreed to on the call.

Based on the milestones established, BioLINCC will send automatic reminders for upcoming milestones through the Study's BioLINCC account. It is the responsibility of the Study to inform BioLINCC of any changes to the milestones in a timely manner. Missed milestones typically result in delays and have resulted in the termination of transfers.

### **6.5.2 SIGNING THE MATERIAL TRANSFER AGREEMENT AND SUBMITTING A PILOT SHIPMENT**

All transfers require the submission of a pilot shipment of biospecimens to assess the physical condition of the biospecimen vials and labels and the accuracy of the inventory file. Prior to arranging a pilot shipment, the Study must complete the NHLBI MTA. The MTA is generated by BioLINCC using information already provided through the BioLINCC account. The Study will be instructed to download the MTA, obtain the appropriate signatures and upload the signed MTA to their BioLINCC account. Materials cannot be transferred to the Biorepository until the MTA has been signed by the appropriate Study signatories and NHLBI staff, and posted in the Study application on BioLINCC.

### **6.5.3 PILOT SHIPMENT**

Following completion of the MTA, the Study will be informed through BioLINCC of the steps to arrange a pilot shipment of biospecimens. Shipping expenses will generally be paid for by the Study and the Biorepository can provide shipping materials.

Prior to scheduling the pilot shipment, the Study will be asked to send a current electronic file of the biospecimen inventory to enable BioLINCC to select a representative sample of specimens. The pilot shipment will typically consist of between 300 and 800 specimens and include all material types and storage conditions, time points, and collection sites. A listing of the biospecimens to include in the pilot shipment will be provided through the BioLINCC website and the Study will arrange the transfer of the listed vials with the Biorepository staff. Shipments will be scheduled to occur on Mondays, Tuesdays or Wednesdays and on a date convenient for both the Study and the Biorepository.

Of note, a manifest of the vials must be included with the shipment and an electronic copy of this manifest must be sent to the Biorepository at the time of shipment. The Biorepository can provide shippers and shipping protocols, if requested.

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 the Study and will include discrepancies and recommended corrective actions.

BioLINCC will schedule a call with the NHLBI PO(s), the Study PI(s) and the key Study members to discuss the pilot shipment report. During this call the timeline and milestones will be reviewed and adjusted if needed. Discrepancies found during the pilot shipment will require correction prior to transfer of the full collection. Discrepancies that cannot be resolved with the Study may result in delays or the withdrawal of the approval to transfer the collection.

### **6.5.4 DATA SUBMISSION**

Prior to the transfer of the collection, clinical data must be submitted to BioLINCC (see sections 5.2 and 5.3 for materials required in a data submission). In addition to the required documentation stated in section 5.2, the study protocol included in the data submission should be the final version and should be accompanied by a summary of changes from previous protocol versions. A road map document that would serve to guide a researcher unfamiliar with the data must be included in the submission and should include such information as a listing of the submitted materials; the names of datasets, their function, and their source(s); guidance/code for importing and using the data; and a list of any changes made to redact/modify variables from their original state.

As stated in section 5.3, pre-redacted, private clinical data and a linking file that allows the specimens to be associated with the data must be provided. For studies that have published, the

data submitted to BioLINCC will need to be reflective of the data reported in the primary manuscript. This can be accomplished by including a frozen set of data used at the time of the primary manuscript, in addition to final adjudicated data. Alternatively, variables can be included in the data that indicate the study population(s) used in the primary manuscript.

BioLINCC will review the submission for completeness of the documentation and clarity of the data. BioLINCC will verify that all specimens in the proposed collection transfer can be linked to the submitted data and that these specimens are properly consented for future use by researchers who would be requesting them through the BioLINCC website. BioLINCC will also assess the replicability of the tables in the primary manuscript using the submitted data.

## **6.6 RELOCATION OF THE BIOSPECIMENS TO THE NHLBI BIOREPOSITORY**

Approval to transfer the collection will be made following the successful completion of the pilot shipment and the receipt and review of the full Study data and documentation. Biospecimens will not be transferred to the Biorepository until the Study data have been accepted for inclusion in the Data Repository.

The facility storing the Study collection will receive a request via BioLINCC to initiate discussions to finalize the arrangements to transfer the collection. Typically, a conference call with Study staff to discuss the details will be arranged. Biorepository contract staff will provide guidance on packing, shipping and logistics. Transfer expenses will generally be paid for by the Study.

Upon receipt, a subset of the collection will undergo the same inspection and reporting process as described for the pilot shipment (Section 6.5.3). The Study site and data management center must be able to provide corrective actions for any discrepancies found during the inspection process.