The BioLINCC Handbook

A Guide to the NHLBI Biologic Specimen and Data Repositories

https://biolincc.nhlbi.nih.gov

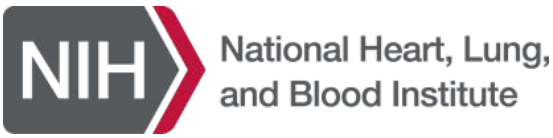

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TABLE OF CONTENTS

1.0 BIOLOGIC SPECIMEN AND DATA REPOSITORIES INFORMATION COORDINATING CENTER 1
1.1 OVERVIEW 1
1.2 BIOLINCC 2
1.3 BIOLOGIC SPECIMEN REPOSITORY (BIOREPOSITORY) 2
1.3.1 OVERVIEW 2
1.3.2 AVAILABILITY OF BIOSPECIMENS 2
1.4 DATA REPOSITORY 3
1.4.1 OVERVIEW 3
1.4.2 AVAILBILITY OF DATA SETS 4
2.0 THE BIOLINCC WEBSITE: STRUCTURE AND FUNCTION 4
2.1 OVERVIEW 4
2.2 THE BIOLINCC HOME PAGE – PUBLIC INFORMATION 5
2.2.1 MAIN MENU 6
2.2.2 LOG-IN/REGISTRATION 6
2.2.3 STUDY WEBPAGE SEARCH 7
2.2.4 FULL WEBSITE SEARCH 7
2.2.5 FEATURED AND RECENT NEWS 7
2.3 STUDY DESCRIPTION PAGE 7
FIGURE 2.2: EXAMPLE STUDY DESCRIPTION PAGE 9
2.4 MY BIOLINCC – THE PRIVATE WORKSPACE AREA 10
2.5 WEBSITE TECHNICAL INFORMATION 10
3.0 REQUESTING BIOSPECIMENS AND DATA 11
3.1 OVERVIEW 11
3.2 STEPS FOR REQUESTING BIOSPECIMENS AND DATA 12
3.3 REVIEWING BIOSPECIMEN REQUESTS 15
3.3.1 OVERVIEW 15
3.3.2 ETHICAL, MATERIAL/VOLUME SUITABILITY AND “COLLECTION IMPACT” REVIEW 16
3.3.3 SCIENTIFIC REVIEW FOR REQUESTS WITH EXISTING FUNDING 17
3.3.4 SCIENTIFIC REVIEW PERFORMED BY A FUNDING GROUP 18

3.3.5 RESEARCH MATERIAL DISTRIBUTION AGREEMENT (RMDA) 18
3.4 REVIEWING REQUESTS FOR DATA SETS 19
3.4.1 OVERVIEW 19
3.4.2 DATASET REVIEW COORDINATED BY BIOLINCC 19
3.5 APPROVED USERS AND COLLABORATORS 19
3.6 AFTER REQUEST FULFILLMENT 20
3.6.1 PROGRESS REPORTS 20
3.6.2 RMDA EXPIRATION AND RENEWAL REQUESTS 20
4.0 PREPARATION AND SUBMISSION OF DATA REPOSITORY DATASETS AND DOCUMENTATION 21
4.1 OVERVIEW 21
4.2 PREPARATION AND SUBMISSION 21
4.3 STUDY DATA FOR A PROPOSED BIOSPECIMEN TRANSFER 25
5.0 PREPARATION AND TRANSFER OF AN NHLBI FUNDED BIOSPECIMEN COLLECTION TO THE NHLBI BIOREPOSITORY 25
5.1 OVERVIEW 25
5.2 REQUESTING TO TRANSFER BIOSPECIMENS TO THE NHLBI BIOREPOSITORY 27
5.3 SUBMITTING AN APPLICATION TO TRANSFER BIOSPECIMENS TO THE NHLBI BIOREPOSITORY 28
5.3.1 REGISTERING THE STUDY TO INITIATE THE APPLICATION 28
5.3.2 SUBMITTING THE APPLICATION DOCUMENTS 29
5.4 REVIEWING THE APPLICATION TO ASSESS THE SCIENTIFIC UTILITY AND TECHNICAL QUALITY OF THE BIOSPECIMEN COLLECTION 30
5.5 TRANSFERRING A COLLECTION TO THE NHLBI BIOREPOSITORY 31
5.5.1 INITIATING THE TRANSFER 31
5.5.2 SIGNING THE MATERIAL TRANSFER AGREEMENT PRIOR TO PILOT SHIPMENT 31
5.5.3 PILOT SHIPMENT 32
5.5.4 DATA SUBMISSION 32
5.6 RELOCATION OF THE BIOSPECIMENS TO THE NHLBI BIOREPOSITORY 33
6.0 MAINTENANCE OF THE NHLBI BIOREPOSITORY COLLECTIONS 33
6.1 OVERVIEW 33
6.2 DATA SOURCES TO ASSESS SCIENTIFIC UTILITY 34
6.2.1 OVERVIEW 34
6.2.2 STUDY CATALOG 34

6.2.3 BIOLINCC REQUEST METRICS 35
6.3 ASSESSING COLLECTIONS FOR SCIENTIFIC UTILITY 36
6.3.1 OVERVIEW 36
6.3.2 SELECTING COLLECTIONS FOR REVIEW 37
6.3.3 PREPARING ASSESSMENT REPORTS 37
6.3.4 BCRP REVIEW 38
6.3.5 ASSIGNING THE NEXT REVIEW DATE 39
6.4 EFFICIENTLY MAINTAINING FREEZER SPACE 39
6.4.1 OVERVIEW 39
6.4.2 USING INFORMATION TECHNOLOGY TO VISUALIZE FREEZER SPACE 39
6.5 PROMOTING RESOURCE USE 43
6.5.1 OVERVIEW 43
6.5.2 BIOLINCC WEBSITE 43
6.5.3 ENGAGING THE SCIENTIFIC COMMUNITY 44
6.5.4 DISTRIBUTING PROCEDURES AND RESULTS 44

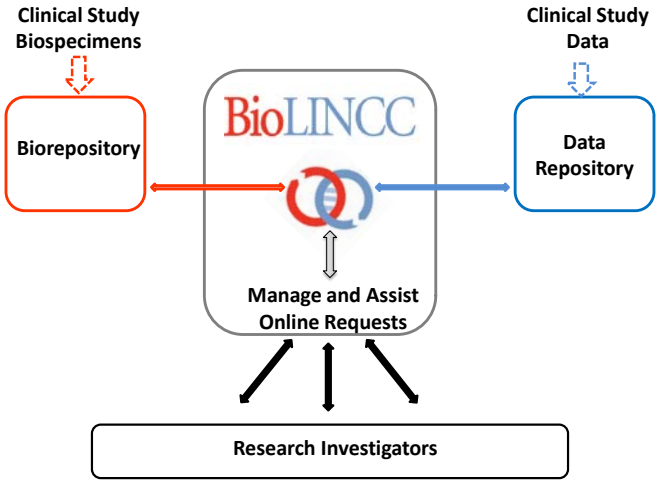
1.0 BIOLOGIC SPECIMEN AND DATA REPOSITORIES INFORMATION COORDINATING CENTER

1.1 OVERVIEW

The National Heart, Lung, and Blood Institute (NHLBI) is one of 27 Institutes and Centers at the US National Institutes of Health. The Institute provides global leadership in the prevention and treatment of heart, lung, and blood diseases and supports basic, translational and clinical research in these areas. In 2007 the NHLBI established a Strategic Plan structured around three goals: Goal 1: Form to function; Goal 2: Function to cause; and Goal 3: Cause to cures. Two strategies to accomplish these goals were *"to develop and facilitate access to scientific research resources"* and *"increase the return from NHLBI population-based and outcomes research".*

In accordance with the 2007 goal-based strategies, the NHLBI established the Biologic Specimen and Data Repositories Information Coordinating Center (BioLINCC) in 2008 to expand the utilization of two unique research resources developed and maintained by the NHLBI. These resources are the NHLBI Biologic Specimen Repository (Biorepository), which has been managed by the Division of Blood Diseases Resources since 1975, and the NHLBI Data Repository, which has been managed by the Division of Cardiovascular Sciences 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.

Figure 1.1: Facilitating Access to NHLBI Biospecimens and Data



1.2 BIOLINCC

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

BioLINCC has been funded under contract since September 2008. During the first year of program initiation, 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 developed. The public web site at https://biolincc.nhlbi.nih.gov/ was launched in October 2009 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 approval processes and an automatic query system to collect information on research progress and publications. Details of the communication portal are provided in Chapter 2 of this handbook. More information about the development of the BioLINCC program and its methods may be found at the following site: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4559201/

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 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

The biospecimens in the Biorepository are considered "open"; that is, the collection is under the custodianship of the NHLBI. The NHLBI is responsible for reviewing and approving requests for biospecimens 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 how to request biospecimen 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 the Data Repository. The Data Repository is managed by the Epidemiology Branch in the Division of Cardiovascular Sciences and includes individual level data on hundreds of thousands of participants from more than 145 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 AVAILBILITY 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 are 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 4 provides information on accessing datasets in the Data Repository.

Please note that BioLINCC provides only complete Study data packages. It does not create custom datasets.

2.0 THE BIOLINCC WEBSITE: STRUCTURE AND FUNCTION

2.1 OVERVIEW

The BioLINCC website is accessed at https://biolincc.nhlbi.nih.gov/.

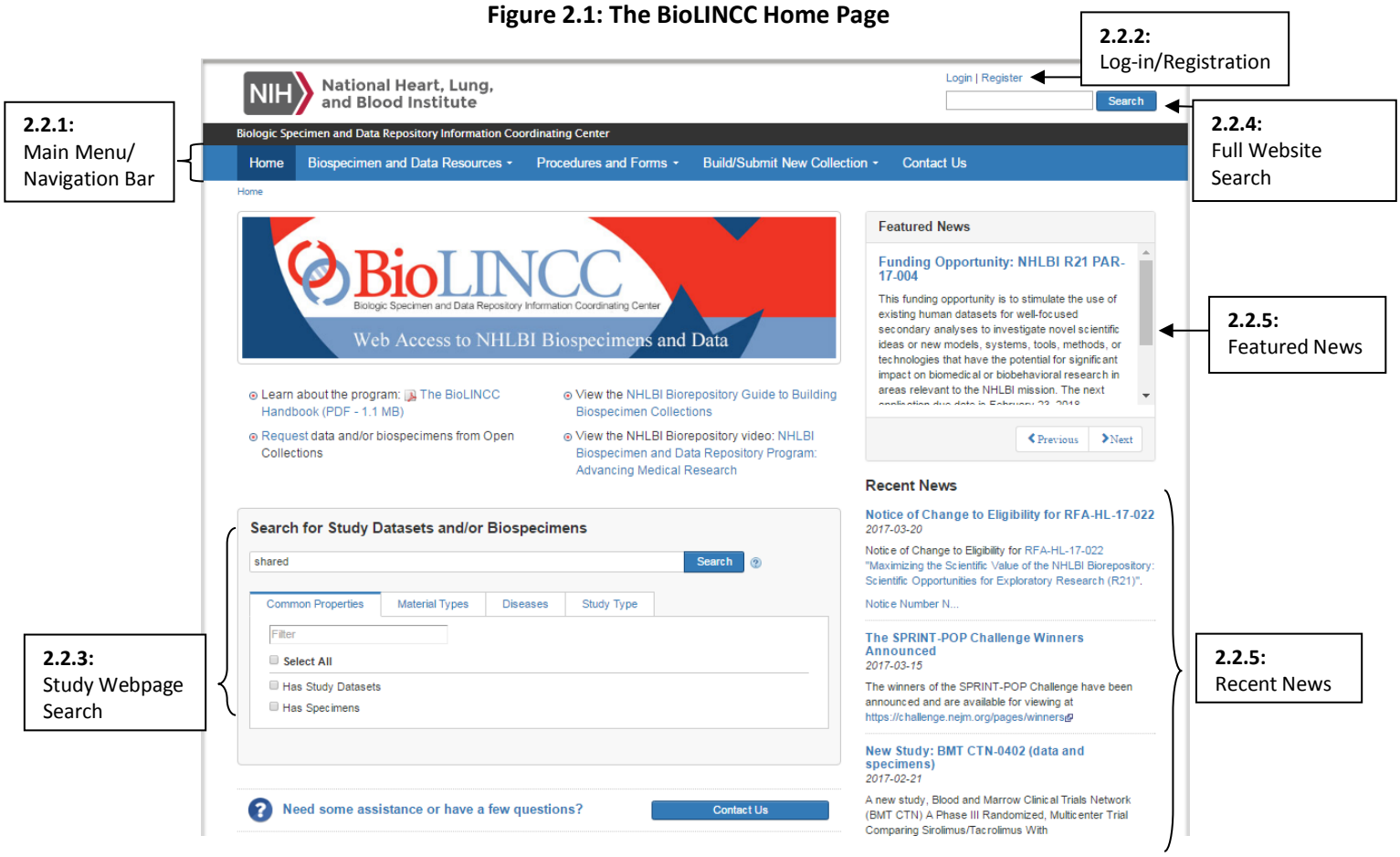
This website is the primary interface with the NHLBI Biologic Specimen and Data Repositories Information Coordinating Center (BioLINCC). The system is comprised of two levels: public information which is available to all users, and a private workspace which is available to registered users.

The public website provides a wealth of information on historical NHLBI clinical and epidemiologic studies which have data or biospecimens in the NHLBI repositories, and includes 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 as shared resources, BioLINCC forms and templates, 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

Figure 2.1: The BioLINCC Home Page



2.2.1 MAIN MENU

The navigation bar at the top of any BioLINCC page provides access to the various sections of the website including the **Home** page, **Biospecimen and Data Resources**, **Procedures and Forms**, **Build/Submit New Collection**, and a section to **Contact Us**.

Next to the **Home** section is the **Biospecimen and Data Resources** section that contains information about BioLINCC and Non-BioLINCC resources. **Overview** provides a brief description of the resources listed on the website. Like the Home page, visitors can search **Studies** that are available for request using search term(s) or one of the available filters. Visitors can explore the **Teaching Datasets** which have been developed as educational tools or the **Public Use Datasets** which are freely available datasets for research purposes. Researchers with an existing NHLBI BioLINCC data set use agreement which is expiring may submit a request to **Renew an Existing Data Use Agreement**. This section also provides links to information about **Publications** stemming from BioLINCC resources and to **Funding Opportunities** that may be applicable to research using BioLINCC resources. Finally, an index is provided for select **Non-BioLINCC Resources**; these are not maintained by BioLINCC but are available for request though external sites.

The **Procedures and Forms** section includes a link to the **BioLINCC Handbook**, as well as links to the **Forms** and **Agreement Templates** used for biospecimen and/or data requests, the Research Materials Distribution Agreement (RMDA) for outgoing requests, and the Material Transfer Agreement (MTA) for the incoming biospecimen collection process. Please note these templates are for informational use to view their components; agreements used in the actual request process will be custom-generated by BioLINCC.

The **Build/Submit New Collection** section is primarily for Parent Study researchers of NHLBI funded studies who are preparing to **Submit Datasets** or **Submit Biospecimens and Datasets** for use as shared resources. Included in this section is a downloadable document entitled "The NHLBI Biorepository Guide to Building Biospecimen Collections for Study and Future Research Use" and a short video highlighting the benefits of creating a quality biospecimen collection to serve as a valuable research resource.

Lastly, users can **Contact Us** at BioLINCC with questions or comments via an online form, e-mail, or through the other contact means listed.

2.2.2 LOG-IN/REGISTRATION

Visitors wishing to request biospecimen or data resources, renew an existing data set agreement or register to submit a new biospecimen collection must become registered users in order to access these private workspaces. The log-in and account registration links are located on the upper right part of the 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, 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 link. Requests for password/username reminders may be submitted though the log-in webpage. Once logged in as a registered user, the section called **My BioLINCC** appears on the navigation bar and allows users to view their saved and submitted requests and to access request-specific communications.

2.2.3 STUDY WEBPAGE SEARCH

The study webpage search utility, located on the BioLINCC home page and on the Studies 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), 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 any BioLINCC 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 FEATURED AND RECENT NEWS

News items are posted to announce the availability of new studies or study updates, and to provide notifications of special events and funding opportunities. If there is more than one featured news item, each item will cycle through the display carousel automatically, or manually using the “previous” and “next” buttons. Recent news items are displayed below any featured news items with a link at the bottom of the section to view older news items.

2.3 STUDY DESCRIPTION PAGE

Each study with resources available on BioLINCC has a description page, which can be accessed from the Studies page. These pages provide a variety of information regarding the study, including **Basic Study Information**, such as the study type and period, as well as a **Study**

Description that provides an overview of the rationale, methodology, and findings of the study as originally conducted. BioLINCC users may also initiate a request for available resources from this page. Figure 2.2 illustrates the typical layout of a study page where data and biospecimens are available.

The **Consent Restrictions** box displays whether there are any restrictions for the type of research that may be conducted using the data and/or biospecimens. In some cases, restrictions may make a request ineligible for fulfillment. In the example shown in Figure 2.2, biospecimens from the ACCESS collection may be used only for sarcoidosis-related research, and therefore requests for use of biospecimens in other areas of research would be denied. In other cases, materials from only the subset of subjects who consented to the proposed research type would be provided. For example, for studies with commercial use data restrictions, investigators requesting data for commercial use would be eligible to receive only the subset of the overall dataset that was provided by subjects who consented to commercial research.

The **Additional Details** sections at the bottom of the description are available for studies linked to biospecimens in the Biorepository. These sections can each be expanded to view more detailed information regarding the study subjects and biospecimens included in the collection. The Study Population tables provide information regarding the number of study participants by age, sex, race, and treatment arm who are included in the study data. Some collections from transfusion-related studies have a limited set of data (referred to as "characterization data"); for these studies, tables display the available biospecimens for subjects by study visit and material type. These numbers are regularly updated and are provided to help interested investigators get a sense of whether the collection may have sufficient materials for the proposed research. Specific biospecimen availability will be provided by BioLINCC staff during the request process in accordance with the requestor's subject and specimen criteria (see section 3.2) and availability is subject to review by the NHLBI, BioLINCC, and the NHLBI Biorepository.

The **Study Catalog** (see also section 6.2.2) is available for studies with biospecimens, and provides an alternative format for viewing key study information. Publicly available sections include the Basic Study Information, Study Consent, Additional Study Information, Study Population (where applicable), and Available Biospecimens.

The **Study Publications** link the user to the database of publications associated with available BioLINCC resources, subset by the particular study being viewed. This is not an exhaustive list of publications, but can provide users with more information on the types of published research that have been conducted using BioLINCC data and/or biospecimens.

FIGURE 2.2: EXAMPLE STUDY DESCRIPTION PAGE

Basic Study Information

A Case Controlled Etiologic Study of Sarcoidosis (ACCESS)

Study Type	Collection Type	Study Period
Epidemiology Study	Open BioLINCC Study *See bottom of this webpage for request information*	June 1995 - March 2003
NHLBI Division	**Date Prepared**	**Last Updated**
DLD	October 1, 2008	December 21, 2005
Clinical Trial URLs	**Primary Publication URLs**	**Study Website**
http://www.clinicaltrials.gov/ct...	N/A	N/A

Consent Restrictions

Consent

- Commercial Use Data Restrictions: No
- Data Restrictions Based On Area Of Research: No
- Commercial Use Specimen Restrictions: No
- Non-Genetic Use Specimen Restrictions Based On Area Of Use: Yes
- Genetic Use Of Specimens Allowed?: Yes
- Genetic Use Area Of Research Restrictions: Yes
- Specific Consent Restrictions
  Biospecimen research is restricted to studies related to sarcoidosis. Use of data is unrestricted.

Study Description

Objectives

To determine the etiology of sarcoidosis by establishig a case control, multi-center study. In addition to etiology, this study also sought to examine socioeconomic variables and the clinical course of patients with sarcoidosis, including quality of life.

Background

Sarcoidosis is a chronic granulomatous disorder of unknown cause that is characterized by activation of T-lymphocytes and macrophages. For many years sarcoidosis was presumed to be an atypical manifestation of tuberculosis because of the similarity between the inflammatory responses of the two diseases. However, as culture techniques became more widely employed to diagnose tuberculosis and it became less common, it became clear that sarcoidosis was not simply a variation of tuberculosis. Data on the etiology of sarcoidosis have come from diverse sources: in clinical investigations, alveolitis has been found to precede granulomatous inflammation; in case control studies, familial aggregation has been identified; and in case reports, recurrence of granulomatous inflammation has been observed after lung transplantation. The cause may not prove to be a single, known exposure. Interactions of exposures with genetic dispositions could have important implications for our understanding of immune responses as well as the pathogenesis of sarcoidosis.

Subjects

736 patients with sarcoidosis enrolled within 6 months of diagnosis from 10 clinical centers in the U.S. Using the ACCESS sarcoidosis assessment system, organ involvement was determined for the whole group and for subgroups differentiated by sex, race, and age (<40 or 40 and older). Cases were matched with a control, and there was a two-year follow-up on cases. The ACCESS group proposed an instrument fo defining organ involvement in sarcoidosis. Biological specimens included DNA, plasma, and bronchoalveolar lavage samples were obtained. The data set includes 718 cases, 686 controls, and two-year follow-up data on 241 cases.

Conclusions

The initial presentation of sarcoidosis is related to sex, race and age, and it tends to remain stable over two years in the majority of patients. The etiology is probably multifactoral with both genetic and environmental factors contributing.

Additional Details

- Study Population
- Available Biospecimens

Subject and Biospecimen Tables

Requests for Open BioLINCC Studies are submitted through this website. Click the Request button to begin.

Request Specimens and/or Data

Request Specimens and/or Data

Resources Available

Specimens and Study Datasets

Study Catalog

Study Catalog

Study Publications (8)

Study Publications

Materials Available

BRONCHIAL LAVAGE
DNA
PERIPHERAL BL MONO CELLS
PLASMA
More Details

Study Documents

- Data Dictionary (PDF - 1.9 MB)
- Procedures Manual (PDF - 98.5 MB)
- Protocol (PDF - 2.9 MB)
- Forms

Study Documents

Persons using assistive technology may not be able to fully access information in the study documents. For assistance, Contact BioLINCC and include the web address and/or publication title in your message. If you need help accessing information in different file formats such as PDF, XLS, DOC, see Instructions for Downloading Viewers and Players.

The **Study Documents** are a key source of information for understanding the study and available data. The Data Dictionary is a standard file generated by BioLINCC that includes a listing of all dataset variables available in the study data package. Users can search this file, potentially in conjunction with study forms which may be annotated with the variable names, to determine whether the data required for a project is included prior to submitting a request. Studies with only biospecimens available may still have a data dictionary that includes biospecimen characterization data. Other posted study documents will vary, but typically include a protocol and/or manual of procedures, forms, and other essential documents.

2.4 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 Studies, Teaching Datasets, Public Use Datasets, and Data Renewal Requests (for expiring existing data agreements). 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 More button near the upper right of the submitted request pages.

2.5 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

3.1 OVERVIEW

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 3.1 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

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 the Biospecimen and Data Resources/Overview or /Studies dropdown page, 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 to provide a nickname for the request and for support information. The study to be requested automatically defaults to the study which was requested on its study webpage, but additional studies can be requested by clicking on the Study field under Request Details, which will bring a full list of available collections for multi-Study selection. The researcher is prompted for information on the study protocol or proposed research plan, whether the results will be used for a commercial purpose, 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 Data Repository Program Officer 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 made available to the requestor as secure transfers through the website, and the requestor is notified when the transfer link is activated. (Note that 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
- Brief overview of the request, including the research rationale, main hypothesis and research aims
- 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 and the determination of the "impact" of the request on the collection (see Section 3.3.2 and Table 3.2).

Requests that are inactive for three months are administratively closed. They may be reopened by the requestor by logging into BioLINCC, and opening the request, and making a comment.

Table 3.2 "Impact": Definitions and Review Options

Impact on the Collection	Definition	Review Options
Low Impact	Not a limited resource *After current request fulfillment 4 or more new requests can be supported based upon historic use (e.g., volume/quantity).* *For biospecimens that are considered abundant and not unique, the 4 or more request restriction is not imposed.*	Funding group or Biorepository scientific expert review. NHLBI staff will be consulted if questions regarding the scientific use of the biospecimens arise.
High Impact	Unique and limited resource *After current request fulfillment, 3 or fewer new requests could be supported based upon historic use (e.g., volume/quantity)*	A panel of scientific experts (e.g., NIH SRG or NHLBI Staff with the appropriate scientific expertise.) NHLBI staff may be consulted when the last aliquot from a collection time point is requested.

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), acceptance of the search results by the researcher, and the availability of funds for the project, the request is formalized. A scientific review is performed in accordance with the processes and impact levels described in Section 3.3.2.

Applicants that do not have funds available upon acceptance of search results 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.

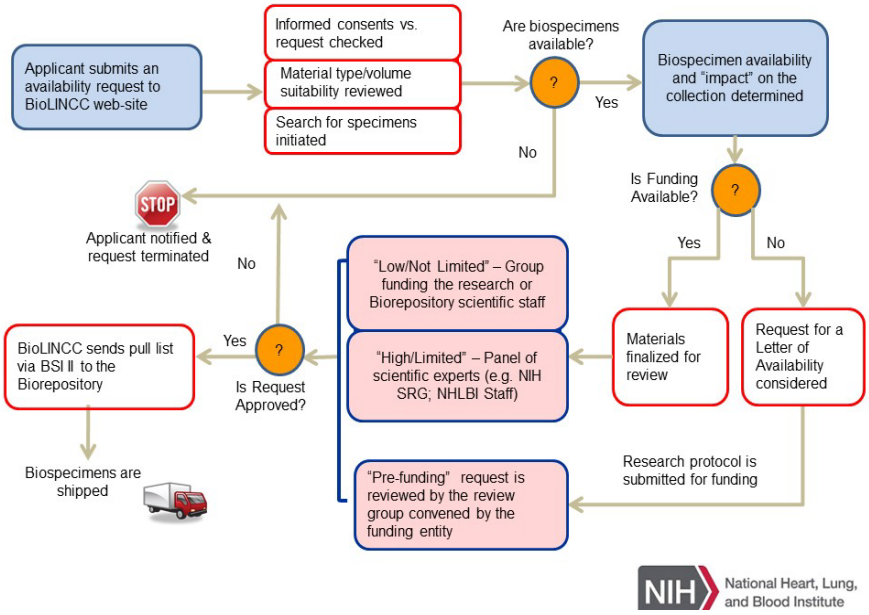
3.3 REVIEWING BIOSPECIMEN REQUESTS

3.3.1 OVERVIEW

All requests for biospecimens undergo a review following the process illustrated in Figure 3.1. There are two review pathways:

- 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 elements:

- 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
- Availability of funding and adequate facilities to perform the research
- 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

All requests for unique and limited biospecimens are required to undergo a rigorous scientific review and biospecimens in this category are not made available for exploratory research protocols. The use of the last aliquot for a subject/material type/draw date may require approval by the NHLBI Division that sponsored the Parent Study. Special justification may also be required for the release of unthawed specimens if previously thawed aliquots are available. Upon acceptance of the request for biospecimens the investigator will be asked to complete a Research Materials Distribution Agreement (RMDA). The RMDA template may be viewed here: https://biolincc.nhlbi.nih.gov/media/BioLINCC.RMDA.V02.d20120806.pdf

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

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 includes 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).

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 reviewer(s) based on the "impact" score as described in Table 3.2. If the assigned reviewer is registered on BioLINCC, the review is typically performed though the BioLINCC private website. The reviewer is provided a link to the request materials centralized within a restricted area and the reviewer documents their review directly via the website. Alternatively, the review can be performed outside the BioLINCC website. BioLINCC contacts the reviewer and provides the reviewer with the materials and the review criteria. The reviewer returns their decision to BioLINCC, and BioLINCC documents the review outcome in the private BioLINCC website area.

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?

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 are coordinated by BioLINCC and are performed by the NHLBI Data Repository Program Officer. 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 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.

3.5 APPROVED USERS AND COLLABORATORS

The RMDA holds the Principal Investigator and the signing recipient institution responsible for adhering to the terms of the agreement, including maintaining BioLINCC materials in a secure manner. The Principal Investigator (PI) is responsible for oversight of Approved Users of BioLINCC materials, and the PI may add additional Approved Users within his/her institution at his/her discretion.

If the project involves collaborators from an outside institution, the collaborators must submit and complete a separate BioLINCC request prior to accessing any BioLINCC data and/or biospecimens. For biospecimens, the use of testing labs outside of the recipient institution is in compliance with the terms of the RMDA as long as the lab is under a contractual non-disclosure agreement such that the biospecimens remain within the purview of the Principal Investigator and his/her institution.

3.6 AFTER REQUEST FULFILLMENT

3.6.1 PROGRESS REPORTS

E-mail notifications requesting a Progress Report for the project described in a fulfilled request are sent annually on March 1. Requestors may also submit a Progress Report via their request page at any point after receipt of data. The Progress Report allows requestors to submit information regarding the overall progress of the project, any abstracts or manuscripts that have been submitted or published, whether the project has been completed, and if completed, whether the data have destroyed per the terms of the Research Materials Distribution Agreement (RMDA) (see also section 3.6.2 below). Publication references resulting from the use of BioLINCC materials may be displayed in the Publications section of the BioLINCC website.

3.6.2 RMDA EXPIRATION AND RENEWAL REQUESTS

The RMDA completed for any request involving data is valid for three years from NHLBI signature. BioLINCC staff will send reminders when the agreement is nearing expiration with instructions to renew access or destroy the data. A renewal request (https://biolincc.nhlbi.nih.gov/requests/data-renewal-request/) requires submission of current IRB documentation, which may take the form of the most recent continuing review from the IRB, or submission of a new protocol if continuing reviews have lapsed. Exemptions are also accepted unless otherwise noted in a study's description. Requestors that complete a Renewal Request will also be eligible to receive any updates made to the data.

If the project has been completed or the RMDA has expired with no intent to renew, the requestor must notify BioLINCC that all data residing on personal computers, portable media, or institutional servers have been permanently deleted and any data CDs have been destroyed, in order to close out the agreement. As stated in section 11 of the RMDA, failure to adhere to the terms of the RMDA will be taken into consideration with respect to any future requests for data and/or biospecimens from the NHLBI repositories.

Renewal requests are not applicable if the Principal Investigator of the project has changed or if the project is moving to a new institution. In such cases, an entirely new data and/or biospecimen (as applicable) request must be submitted and completed. Transfer of BioLINCC data to a new institution requires confirmation that any data remaining at the previous institution have been destroyed, or transferred to a new Principal Investigator under a new RMDA.

The RMDA for specimen-only requests does not expire and renewals are not required.

4.0 PREPARATION AND SUBMISSION OF DATA REPOSITORY DATASETS AND DOCUMENTATION

4.1 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:

https://www.nhlbi.nih.gov/grants-and-training/data-sharing-policy-frequently-asked-questions

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 5 for the application process).

4.2 PREPARATION AND SUBMISSION

Three brief checklists and forms have been made available on the BioLINCC Submit Datasets page (https://biolincc.nhlbi.nih.gov/submit_datasets/) to assist Studies in the curation and submission of Study data to the NHLBI Data Repository. These are intended to provide guidance in the preparation of the Study data, and to be submitted as part of an incoming data package.

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.

In addition to the process steps described below, Studies which are applying to transfer biospecimens as well as data are advised to review Section 4.3 for specimen inventory data requirements.

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).

- For Studies applying to transfer a biospecimen collection to the NHLBI Biorepository a data file structured to list one observation for each individual biospecimen sample in the inventory and a data dictionary with a description of the variables and their formats must be provided. The requirements for the data file are provided in the NHLBI Biospecimen Collection Questionnaire, Section H 5, which is posted to the BioLINCC Forms page: https://biolincc.nhlbi.nih.gov/website_forms/.

- **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.

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.

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.

4.3 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 4.2, 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 4.2, 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 5). 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.

5.0 PREPARATION AND TRANSFER OF AN NHLBI FUNDED BIOSPECIMEN COLLECTION TO THE NHLBI BIOREPOSITORY

5.1 OVERVIEW

This Chapter provides information on transferring the custodianship of an NHLBI-funded 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, which is posted to the BioLINCC Forms page (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.

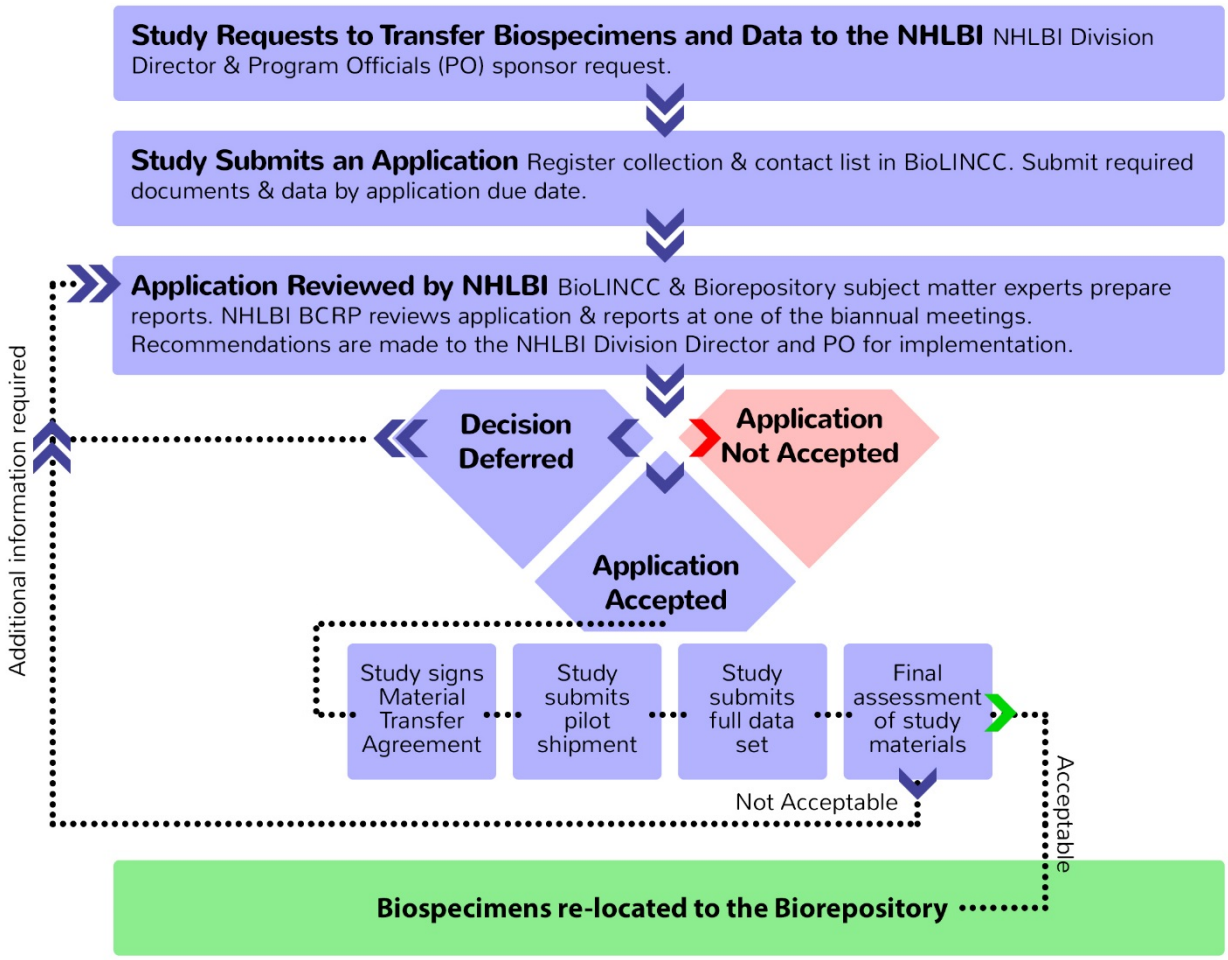
All biospecimen and data collections undergo an assessment for potential scientific utility and quality prior to acceptance into the Biorepository. The quality of a Study collection is based on the completeness of the collection and on the procedures used by the Study to ensure the quality of the biospecimens 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/ 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 biospecimens to the Biorepository to serve as "open" scientific resources through the BioLINCC website. The review is based on information provided by the Study in the Questionnaire as well as 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 5.1 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 5.1: Preparation and Transfer Process



5.2 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 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.

5.3 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 on the BioLINCC Submit Biospecimens and Datasets page: 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.

5.3.1 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 5.2).

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.

5.3.2 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: https://biolincc.nhlbi.nih.gov/website_forms/
- This document includes detailed information regarding the scientific value and technical quality of the collection.
- A SAS or Excel/CVS 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.

5.4 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.

5.5 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.

5.5.1 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.

5.5.2 SIGNING THE MATERIAL TRANSFER AGREEMENT PRIOR TO 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.

5.5.3 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. 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.

5.5.4 DATA SUBMISSION

Prior to the transfer of the collection, clinical data must be submitted to BioLINCC (see sections 4.2 and 4.3 for materials required in a data submission). In addition to the required documentation stated in section 4.2, 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 4.3, 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.

5.6 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 5.5.3). The Study site and data management center must be able to provide corrective actions for any discrepancies found during the inspection process.

6.0 MAINTENANCE OF THE NHLBI BIOREPOSITORY COLLECTIONS

6.1 OVERVIEW

As the custodian of the archived Biorepository collections, the NHLBI has developed standardized procedures to assess the scientific utility of a collection over time and minimize maintenance costs. This Chapter provides information on the data and procedures used to assess scientific utility, the tools and workflows established to efficiently manage the archived samples and strategies to promote resource use.

6.2 DATA SOURCES TO ASSESS SCIENTIFIC UTILITY

6.2.1 OVERVIEW

The biospecimen/data linkage performed by BioLINCC to make biospecimens available online to qualified investigators has enabled the searching and identification of thousands of samples collected on numerous NHLBI funded Studies. In many cases, these assessments show that collections have not been used for research by non-Study investigators, and in other cases collections have not been accessed at all since acquisition. This expanded biospecimen retrieval activity assessment has enabled the development of efficient, data-driven biospecimen management workflows and demonstrated the need to acquire data that can be used to assess a collection's scientific utility. The two data sources used to assess scientific utility are: 1) the BioLINCC Study Catalog, and 2) biospecimen request metrics.

6.2.2 STUDY CATALOG

Practices in specimen collection techniques, preservatives/additives and equipment used, and in labeling and storage have evolved over the five decades during which the collections were built and archived in the NHLBI Repository. The techniques applied for each Study vary among the hundreds of participating recruitment centers and network practices. Leveraging the BioLINCC web platform, both public and private portals were established to centralize biospecimen data collected during the Study and from the linkage of the vials to their phenotypic data, as well as information resulting from fulfilling BioLINCC requests.

The Study Catalog serves as a working catalog and was designed collaboratively by BioLINCC and the Biorepository program staff. The sources of information include the original Study documents, inventory management history, physical observations at specimen intake, observations on retrieval, assay suitability assessments, key data elements used for searching, internal Biorepository control documents and QA/QC results. The Study Catalog is indexed by Study collection and has the following 13 categories (5 public and 8 private facing):

The five public facing categories are:

1. Basic Study Information including the Study name and length of the Study;
2. Study Consent describing use restrictions, if any;
3. Additional Study Information including Study objectives and background;
4. Study Population tables by age, sex, race and treatment; and
5. Available Biospecimens by material type and Study visit.

The eight private facing categories used to assist with processing requests are:

1. Biospecimen Characteristics describing collection and processing methods;
2. Biospecimen Request Processing information including aliquoting schemes and specimen suitability;

3. Informed Consent Considerations by collection center and/or timeframe;
4. Label Considerations including vial label contents and vial label issues;
5. General Quality of Collection from sample retrieval and distribution notes and previous collection QC activities;
6. Specimen Search Data indicating key data variables of interest (variables used in biospecimen request searches);
7. Collection Utility showing past use; and
8. BioLINCC Specimen Identification providing a description of how particular vial discrepancies encountered can be resolved.

Information from both the public and private categories is updated continuously throughout the year in the Study Catalog.

6.2.3 BIOLINCC REQUEST METRICS

A comprehensive set of metrics was developed to track and assess the biospecimen request process. Metrics are gathered throughout the request process and include the number of requests for a given Study Collection and their outcome (were specimens available, were they distributed and if not, why not), the number and type of biospecimens distributed, the number and type of vial discrepancies found during distribution activities and the number of peer review abstracts and publications resulting from biospecimen use. The request data are reviewed and updated throughout the year and made available to the NHLBI through the private BioLINCC web portal.

The data from the request metrics are used to review the scientific utility of a biospecimen collection over time. Collection use is defined as the percentage of biospecimens distributed to BioLINCC requestors. Given that collection size can increase due to aliquoting, the size of the collection is set as the number of samples first posted on the BioLINCC website. If collection size is reduced by the removal of samples with no/low scientific utility, then the original collection size is reduced by the number of samples removed and collection use is re-calculated. This method has been found to accurately identify collections, and parts of collections, with low scientific utility and to not penalize collections with high scientific utility where the number of samples has increased over time due to aliquoting to conserve the collection.

A full description of the metrics and their results from the first six years of sharing biospecimens is in press: Giffen CA, Wagner EL, Adams JT, Hitchcock DM, Welniak LA, Brennan SP, Carroll LE. Providing Researchers with Online Access to NHLBI Biospecimen Collections: The Results of the First Six Years of the NHLBI BioLINCC Program. (PLOS One, 2017, In Press).

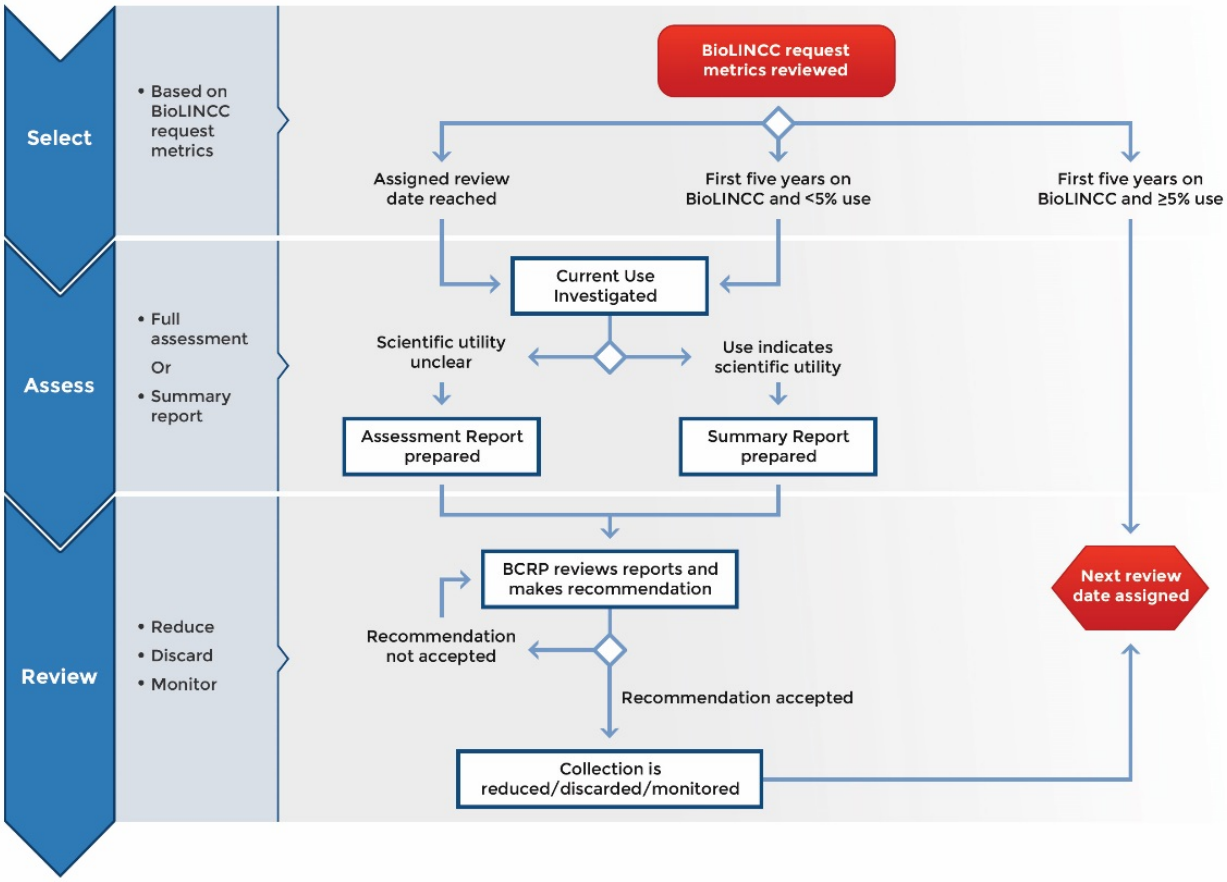
6.3 ASSESSING COLLECTIONS FOR SCIENTIFIC UTILITY

6.3.1 OVERVIEW

The cost of maintaining biospecimen collections is directly related to the number of freezers that are needed to store the samples. Developing strategies to reduce the number of samples with no/low scientific utility enables new collections to be acquired without significantly increasing storage costs. Figure 1 illustrates the three stages that are used to assess the scientific utility of a collection: 1) collection selection; 2) collection assessment and report preparation; and 3) NHLBI review.

The assessment process is a collaborative effort between NHLBI and the BioLINCC and Biorepository programs. The BioLINCC and Biorepository programs provide insight into the use and storage requirements of the collection and these are used by the NHLBI Biospecimen Collection Review Panel (BCRP) to assess scientific utility. BCRP collection assessment meetings are scheduled two times a year and are distinct from the meetings designated to assess incoming collections for transfer to the Biorepository as described in Chapter 6. BCRP recommendations on retaining and/or reducing samples are made to the appropriate NHLBI Division for acceptance. Accepted recommendations are implemented through the BioLINCC and Biorepository programs.

Figure 6.1: Assessing the Scientific Utility of a Biorepository Collection



6.3.2 SELECTING COLLECTIONS FOR REVIEW

Selecting Collections for review is done once a year by the NHLBI using the BioLINCC request metrics described in Section 6.2.3. The following selection algorithm has been developed to ensure that all collections undergo assessments throughout their storage:

Collections that have been available on BioLINCC for at least five years with <5% use and have not been previously assessed are selected. The 5% cutoff is based on historical Biorepository data and has proven to be a sound predictor of scientific utility.

Collections that have already undergone an initial assessment and have reached their next assigned re-evaluation date are selected.

Collections that have ≥ 5% use after their first five years on BioLINCC are not selected for review. These collections and all collections that do undergo an assessment are assigned a future evaluation date which is typically five years in the future.

6.3.3 PREPARING ASSESSMENT REPORTS

Selected collections for review go through an investigation to determine the level of assessment required to determine whether the collection should be discarded, reduced or monitored. Data in the BioLINCC Study Catalog and from the request metrics are prepared and discussed with NHLBI Program Staff familiar with the original Study.

Investigations that indicate that a collection has potential scientific utility and that reduction efforts would be costly given the size and storage configuration of the biospecimens are summarized and presented to the BCRP for discussion. For example, if a collection has had several requests but few requests fulfilled due to lack of funding, then additional monitoring activities may be warranted, given that the cost of reduction may exceed the cost of storage for an additional five years. In these circumstances, a summary of the collection's outgoing request data is prepared for review by the BCRP with a recommendation for developing a targeted promotion plan.

When request metrics indicate that the collection has had no/few requests or that fulfilled requests result in a small percentage of the collection being used, a more comprehensive assessment is performed. An NHLBI Biospecimen Collection Assessment Report is initiated by BioLINCC at the request of the NHLBI. The report consolidates data from the BioLINCC Study Catalog, the request metrics and the physical storage configuration and includes the information described in Table 6.1. The report also includes an evaluation of the specimen material types, completeness of biospecimen inventory and proposed strategies to reduce the number of vials with no/low scientific utility taking into consideration reduction and storage costs. For example, frequently requested collections may lose their scientific utility over time due to a depletion of baseline visit samples. Of note, collections that are not reduced due to cost and continue to

demonstrate low scientific utility will eventually be discarded at a box level. Table 6.1 presents the Assessment Report's key elements and information contents.

The NHLBI BioLINCC and Biorepository Contracting Officer Representatives (CORs) review and finalize the reports. The reports are provided to the BCRP at least two weeks prior to the BCRP meeting.

Table 6.1: NHLBI Biospecimen Collection Assessment Report Format

Report Sections	Information Content
Collection Under Assessment	Parent Study and Collection Name NHLBI Division HIV Relevance Number of years available on BioLINCC Total Available Vials (list number by material type) Percent Use for current and past assessment periods BioLINCC Request Metrics
Parent Study	Basic Study Information (including design and population) Consent Restrictions
Assessment	Summary of Prior Assessment(s) Biospecimen Characteristics Label considerations Collection Utility: • Proposed scientific use from NHLBI Biospecimen Questionnaire, if available • Summary of use for fulfilled requests, including any biospecimen issues identified by the requestor Promotion Activities Conclusion(s).
BCRP Review	Recommendation(s)
Signatures	BCRP Chair NHLBI Division Director

6.3.4 BCRP REVIEW

The BCRP reviews the assessment and summary reports of the selected collections two times a year. Based on their review, the BCRP makes recommendation(s) regarding the reduction, discard or active monitoring of a collection to the Director of the NHLBI Division that originally funded the Study. Active monitoring typically includes targeted promotion. The Division Director

may accept the recommendations or request that additional information be considered. The BCRP Executive Secretary sends questions or issues related to the recommendation(s) to the BCRP for further discussion. Accepted BCRP recommendations are implemented and tracked in the private facing section of the Study Catalog.

6.3.5 ASSIGNING THE NEXT REVIEW DATE

Following the BCRP meeting each collection that was assessed, reviewed or had ≥5% biospecimen utilization after the first five years is assigned a new evaluation date. This date is typically set to occur five years after the prior review.

6.4 EFFICIENTLY MAINTAINING FREEZER SPACE

6.4.1 OVERVIEW

The Biorepository acquires Study collections as bulk transfers at the end of a Study's funding period, at a point where typically freezer boxes have not been consolidated prior to transfer. In addition, non-consecutive unoccupied spaces occur as vials in the stored collections are requested and distributed. Reducing costs by improving storage efficiency has been a goal of the Biorepository program for several years. This goal was accomplished by leveraging the IT expertise at BioLINCC and the biospecimen management expertise at the Biorepository to develop an IT tool that provides a freezer-wide view of vial locations. Using this tool, workflows to efficiently retrieve samples and to consolidate storages boxes that have <75% occupancy levels have been developed and implemented. The results of the initial consolidation effort using this tool have been described: Shea KE, Wagner EL, Marchesani L, Meagher K, Giffen C. Biopreservation and Biobanking. February 2017, 15(1): 17-19. https://doi.org/10.1089/bio.2016.0112. The tool and the workflows used at the Biorepository are described below.

6.4.2 USING INFORMATION TECHNOLOGY TO VISUALIZE FREEZER SPACE

Efficiently managing freezer space requires a full-scope view of the sample handling activities across a biorepository. Knowing how many freezers and storage boxes contain a specific set of biospecimens, how full a storage box is prior to retrieving specimens and what steps are undertaken to locate, remove, and relocate biospecimens is essential when developing tools to improve sample management. With this information, managers can accurately assess the task at hand, explore multiple scenarios to complete the task, and select the strategy which best meets their goals. For example, retrieval 10,000 biospecimens differs greatly in cost and time if the biospecimens are spread over multiple freezers as opposed to grouped together, packed sequentially and spread among a few storage boxes located in two or three freezers. The first case likely demands that a majority of the biospecimens are pulled and identified individually, while the later scenario likely can be accomplished using a box-level retrieval process.

The BioLINCC IT tool developed to visualize space in the Biorepository's freezers uses existing data within the Biorepository's Laboratory Inventory Management System (LIMS). The LIMS tracks label identifiers and detailed location information for each vial/sample. Using this granular location information, a reporting framework was built to work alongside the LIMS. The framework requires that every freezer is mapped based on a set of known dimensions (the number of racks within the freezer and the box capacity of the racks). The mapping and existing LIMS location data can then be queried to generate reports that visualize the space within a freezer and within a storage box. It may also be used to illustrate boxes in which specimens from multiple collections have been co-located.

The tool serves as an access point to gather the user's input, aggregate the necessary information from the LIMS and deliver the final reports to the end-user in conjunction with a dynamic mapping of the location data. The Biorepository manager enters specific biospecimen request parameters and the tool then provides a report detailing the location and density of the set of biospecimens queried. The location information for each specimen is parsed for display as a mapped representation of each freezer detailing every rack and box container within the rack. Each box is displayed as an independent object and visually emphasized by a color gradient based on the results of the user's query within that container, a box with 0 biospecimens of interest appears differently than one with 50 as illustrated in Figure 6.2A and an example of the summary reports (heat maps) generated is illustrated in Figure 6.2B.

Figure 6.2A: Heat Map of Configured Chest Freezer

Freezer Rack #

Freezer Rack Box #

Rack	box_1	box_2	box_3	box_4	box_5	box_6	box_7	box_8	box_9	box_10	box_11	box_12	box_13
001	0	7	2	0	0	0	79	1	0	0	0	0	0
002	0	0	1	1	0	0	0	0	0	1	0	80	96
004	34	36	28	25	34	30	28	9	25	25	30	35	61
005	28	31	40	25	34	55	28	62	57	31	54	43	43
006	31	25	27	26	24	24	30	27	27	24	25	31	57
008	15	40	21	38	29	26	34	24	17	20	20	22	18
010	0	1	0	0	0	0	0	0					
011	0	0	0	0	1	2	0	0					
012	0	0	0	0	0	1	0	0					
013	0	2	2	0	2	2	0	0					
014	3	2	2	1	2	0	0	0					
015	0	0	57	77	79	73	79	79					
018	5	22	20	30	26	29	35	24	30	31	39	20	30
019	31	38	31	18	19	45	30	32	23	26	46	43	21
020	55	52	68	78	78	78	78	77					
021	23	19	19	19	21	24	27	23	23	18	50	46	24
022	59	59			77	71	72						
023	1	1	1	1	2	2	1	2	1	1	21	21	24

The number of free spaces in a box is provided and the color becomes darker as the number of unoccupied spaces increases.

White = Non-available space due to varying rack capacity/box dimensions

Cream ≥90% full box
Black = empty boxes/free space

Figure 6.2B: Example of an IT Freezer Space Tool Summary Table

Box counts by number of unoccupied spaces within

The FREQ Procedure

Unoccupied Spaces Within Each Box				
unoccupied	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Empty	6	1.23	6	1.23
0	62	12.73	68	13.96
1-5	132	27.10	200	41.07
6-10	12	2.46	212	43.53
11-20	32	6.57	244	50.10
21-40	109	22.38	353	72.48
41-60	36	7.39	389	79.88
61+	98	20.12	487	100.00

By-study counts of boxes with at least 41 unoccupied spaces
Rows in yellow indicate boxes with specimens from multiple studies

Unoccupied Spaces	Studies Within Box
Empty	None (Empty)
41-60	(ACT)
41-60	(ARDS 1) ACUTE RESPIRATORY DISTRESS SYNDROME , (ARDS 3) ACUTE RESPIRATORY DISTRESS SY
41-60	(ARDS 2) LASRS, LATE STEROID RESCUE STUDY
41-60	(ARDS 2) LASRS, LATE STEROID RESCUE STUDY , (ARDS 3) ACUTE RESPIRATORY DISTRESS SYNDRO
41-60	(ARDS 2) LASRS, LATE STEROID RESCUE STUDY , (ARDS 3) ACUTE RESPIRATORY DISTRESS SYNDRO
41-60	(HHS) HONOLULU HEART PROGRAM

A simple legend describing the thematic mapping and summary information of the user's results are included in every report detailing the number of containers in which the resulting biospecimen selection is spread across as well as a total count of resulting specimens. Additional details are made available to the user by hovering over any displayed box element to receive details of the query's results within that single container. Options are also included for the user to perform simple modifications to the mapping to enhance usability based on their current needs. The color gradient can be inverted on demand as well as switched between an interpretation of results per box as an absolute count or as a percentage of the containers total specimens. Figure 6.3 illustrates the gradient color changes where storage boxes with few specimens are colored darker that those storage boxes with many. Finer level of data can be accessed by way of clicking on any box element within the visualization. Once clicked, a separate visualization is generated and presented detailing the biospecimen contents of the storage box mapped by the locations data stored within the LIMS. This use of the tool enables a rapid assessment for consolidation at a box, rack, or freezer level. Figure 6.4 illustrates a separate query that can be used to visualize the full-scope of a retrieval task where the storage boxes containing specimens (cream) are scattered in racks across five freezers.

Figure 6.3: Evaluating Freezer and Storage Box Space

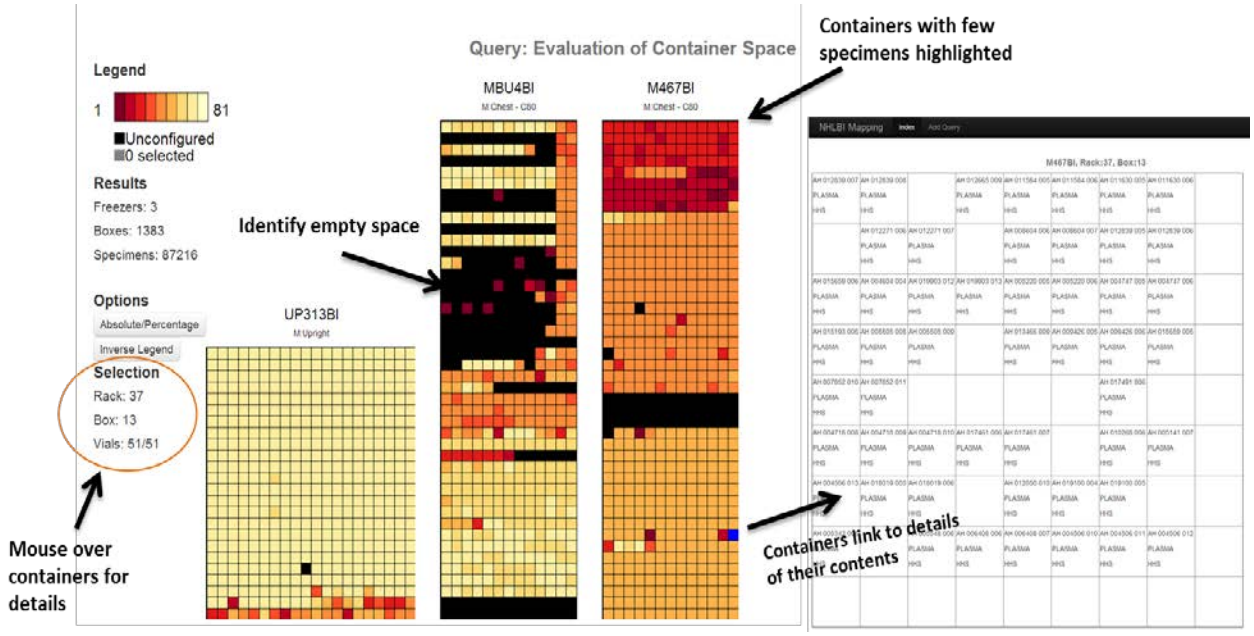
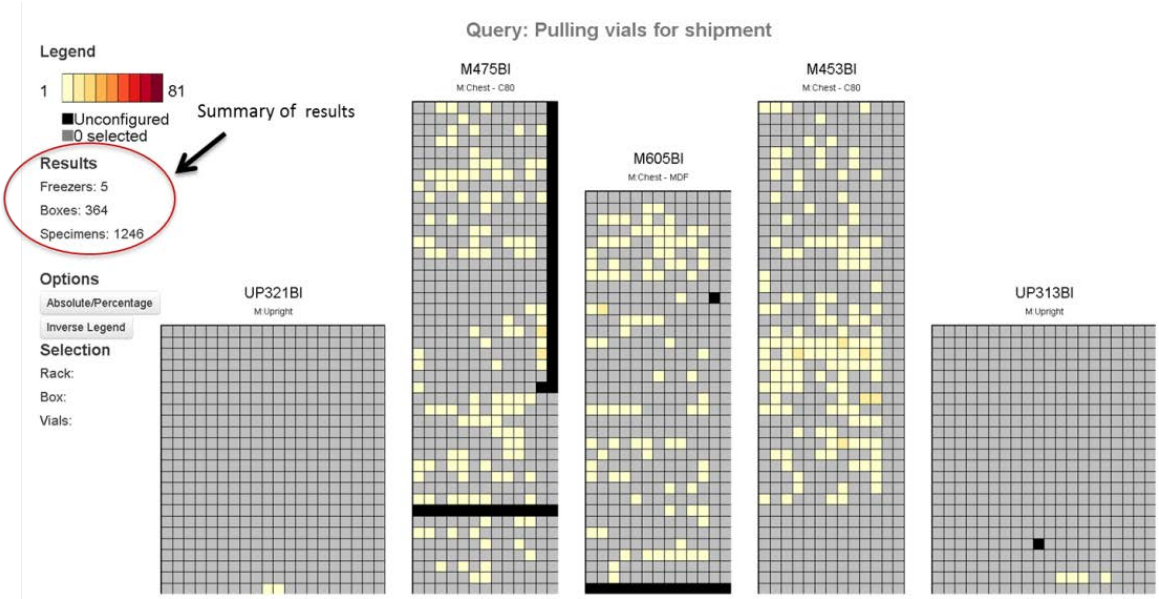


Figure 6.4: Locating Vials for Retrieval Stored Across Multiple Mechanical Freezers



The IT tool and the reports are now part of the Biorepository's standard workflows, thereby improving the efficiency of retrieving vials and consolidating storage box space. The most significant impact to the maintenance of the collections is the ability to now track space within each mechanical freezer and to strategically target freezer consolidation activities.

6.5 PROMOTING RESOURCE USE

6.5.1 OVERVIEW

The primary objective of the BioLINCC program is to maximize the scientific value of historical and contemporary NHLBI biospecimen and data collections by facilitating access to, and promoting awareness of these resources to the scientific research community. The BioLINCC website was designed to accomplish both these objectives in parallel with more targeted promotion activities. The activities described below have succeeded in increasing use and provide an overview for developing strategies to promote scientific resources.

6.5.2 BIOLINCC WEBSITE

The BioLINCC website was launched in October 2009 and is considered the public face of the Biorepository and Data Repository. The website design was carefully developed to be instantly recognizable, highly functional and to comply with NHLBI branding requirements and Federal IT requirements. The website has several features which have been developed and enhanced over the years. These include:

- A search engine to research and identify suitable related resources.
- The BioLINCC Handbook to provide guidance both to requestors seeking research materials and to study groups who wish to deposit resources into the Repositories.
- The NHLBI Biorepository Guide to Building Biospecimen Collections for Study and Future Research Use, and its companion video "The NHLBI Biospecimen and Data Repository Program: Advancing Medical Research" to assist and encourage Studies in building and sharing research resource collections.
- The Study Catalog for biospecimens to provide information on the types of samples available for each Study.
- A searchable publication database containing manuscripts resulting from the use of the biospecimen and data resources.
- A news item webpage and a featured news carousel on the homepage as well as a webpage devoted to other NHLBI funding opportunities for which BioLINCC resources may be appropriate. For example, the release of the NHLBI funding opportunities are publicized by BioLINCC news releases and emails to BioLINCC registered users are sent to highlight new opportunities for research.

The efficiency and flexibility of the website platform has led to the sharing of the open source software with other NIH programs and to collaborative projects with other groups such as the New England Journal of Medicine SPRINT Challenge. The goal of the challenge was to encourage innovative analysis of the SPRINT study primary outcome paper data.

6.5.3 ENGAGING THE SCIENTIFIC COMMUNITY

Attending national and international scientific meetings has proven to be a valuable promotion activity that highlights the availability of the NHLBI biospecimen and data resources. These activities include:

- Development and circulation of a BioLINCC program brochure.
- Focused informational flyers describing available resources by NHLBI Division. These are updated and re-printed as new Study data and biospecimens are added to BioLINCC.
- A portable BioLINCC booth for use at national and international scientific conferences with small and large table-top displays.
- Making a loop of the Biorepository Guide companion video for use at the booth.
- Submitting abstracts and giving oral and poster presentations, and invited speaker symposia at national and international scientific conferences.
- Participation in workshops related to issues in biobanking.

From these meetings, collaborations with several NIH and non-NIH groups have been established and the BioLINCC website cross-links with other groups through its non-BioLINCC resource website page.

6.5.4 DISTRIBUTING PROCEDURES AND RESULTS

Publishing the BioLINCC procedures and results in peer reviewed journals has also assisted in improving awareness of the program and its resources. As of May 2017 the following manuscripts have been published or are in press:

- Giffen CA, Carroll LE, Adams JT, Brennan SP, Coady SA, Wagner EL. Providing Contemporary Access to Historical Biospecimen Collections: Development of the NHLBI Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC). Biopreserv Biobank 2015 Aug;13(4):271-9. Epub 2015 Jul 17. PMC4559201
- Shea KE, Wagner EL, Marchesani L, Meagher K, Giffen C. Efficiently Maintaining a National Resource of Historical and Contemporary Biological Collections: The NHLBI Biorepository Model. Biopreservation and Biobanking. February 2017, 15(1): 17-19. https://doi.org/10.1089/bio.2016.0112
- Coady SA, Mensah GA, Wagner EL, Goldfarb ME, Hitchcock DM, Giffen CA. Use of the National Heart, Lung, and Blood Institute Data Repository. N Engl J Med 2017; 376:1849-1858, May 11, 2017. www.nejm.org/doi/pdf/10.1056/NEJMsa1603542
- Giffen CA, Wagner EL, Adams JT, Hitchcock DM, Welniak LA, Brennan SP, Carroll LE. Providing Researchers with Online Access to NHLBI Biospecimen Collections: The Results of the First Six Years of the NHLBI BioLINCC Program. (PLOS One, 2017, In Press)