



**BERYLLIUM BIO BANK(BBB)**

**PROTOCOL**

**AUGUST 2011**

**NOTICE**

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**BERYLLIUM BIO BANK(BBB)****PROTOCOL****TABLE OF CONTENTS**

<b>CHAPTER</b>	<b>PAGE</b>
1. INTRODUCTION-----	1
1.1 Summary-----	1
1.2 Purpose of the Study Protocol -----	2
2. GOALS, BACKGROUND AND SIGNIFICANCE -----	4
2.1 Specific Goals -----	4
2.2 Background and Significance -----	5
2.3 Study Design -----	6
3. STUDY POPULATION AND PROTECTION OF HUMAN SUBJECTS-----	9
3.1 Introduction -----	9
3.2 Eligibility Criteria -----	9
3.2.1 Inclusion Criteria-----	10
3.2.2 Exclusion Criteria-----	10
3.2.3 Case Definitions -----	10
3.3 Recruitment Strategies -----	12
3.4 Recruitment Goals -----	14
3.5 Informed Consent -----	15
3.6 HIPAA Compliance -----	17
3.7 Potential Risks-----	17
3.8 Data Safety and Monitoring Plan and Adverse Events-----	21
4. CLINICAL CENTER PROCEDURES-----	24
4.1 Overview-----	24
4.2 Interviews and Questionnaires-----	25
4.2.1 Medical and Family History-----	25
4.2.2 Exposure History-----	25
4.3 Biological Specimen Collection-----	26
4.3.1 Overview of Biological Specimen Collection-----	26
4.3.2 Role of the Specimen Core Laboratory-----	27
4.3.3 Overview of Tissue Specimen Acquisition-----	27
4.3.4 Acquisition of Fixed Tissue Specimens-----	28

4.3.5	Tissue Labeling and Supplemental Information-----	28
4.3.6	SCL Reference Slides-----	29
4.3.7	Blood specimen acquisition-----	29
4.3.8	Bronchoalveolar lavage fluid and cell specimen acquisition---	29
4.4	Imaging Studies-----	30
4.4.1	Computed Tomography (CT) Scans-----	30
4.5	Medical Record Data Abstraction-----	31
4.5.1	Pathology reports-----	33
4.5.2	Radiology interpretations-----	33
4.5.3	Pulmonary Function Tests-----	34
4.5.4	Lung Volume Measurements-----	34
4.5.5	Exercise Tests-----	35
4.5.6	Arterial Blood Gas-----	37
4.5.7	Diffusing Capacity for Carbon Monoxide (DLCO)-----	37
4.5.8	Clinical Laboratory Data-----	38
4.6	Data Entry -----	38
5.	CORE LABORATORY PROCEDURES-----	41
5.1	Overview of Cores-----	41
5.2	Specimen Core Laboratory (SCL)-----	41
5.2.1	Shipment and Tracking of Samples -----	41
5.2.2	Specimen Collection and Processing -----	42
5.2.3	Tracking receipt of specimens -----	43
5.2.4	Processing of specimens-----	43
5.2.5	Storing of blood specimens-----	43
5.2.6	Redistribution of specimens-----	44
5.3	Genetics and Plasma Core Laboratory (GPCL) -----	45
5.3.1	Shipment and Tracking of Data -----	45
5.3.2	Specimen Collection and Processing -----	45
5.3.3	Tracking receipt of specimens -----	46
5.3.4	Processing of specimens-----	46
5.3.5	Storing of DNA specimens-----	46
5.3.6	Redistribution of DNA and plasma specimens-----	47
6.	Data Collection and Management-----	49
6.1.	Internet Data Management System (IDMS) Overview-----	49
6.2.	IDMS Core Security Dimensions-----	50
6.2.1.	Authentication and Authorization-----	50
6.2.2.	Nonrepudiation-----	52
6.2.3.	Data Integrity-----	52
6.2.4.	Confidentiality-----	53
6.2.5.	Backup / Recovery, and Availability-----	54
6.3.	Security Policies Documentation-----	54
6.3.1.	Security Policies and Procedures-----	54
6.3.2.	Risk Assessment and Mitigation-----	55

6.3.3.	Disaster Recovery Plan-----	55
6.3.4.	Auditing Policies and Procedures-----	56
6.4.	Quality Control and Assurance-----	56
6.4.1.	Studies and Reports-----	56
6.4.2.	Clinical Coordinators-----	58
6.4.3.	Core Laboratories-----	59
6.4.4.	Data Coordinating Center-----	59
6.4.4.1.	IDMS-----	59
6.4.4.2.	Clinical Site Visits-----	61
6.4.5.	BBB Investigators-----	63
6.4.5.1.	DCC Site Visits-----	63
6.5.	Data Collection Forms-----	64
6.5.1.	Paper Forms Validation Rules-----	64
6.5.2.	Form Revisions-----	64
6.6.	Core Laboratory Data Management-----	65
6.6.1.	Specimen Tracking-----	65
6.6.2.	On-site Monitoring-----	66
6.7.	CT Image Data Management-----	67
6.7.1.	Data Acquisition, Shipment, and Tracking Data-----	67
6.7.2.	Software Considerations-----	67
6.7.3.	Hardware Considerations-----	68
6.7.4.	Image Acquisition and Initial Clinical Center Storage-----	68
6.7.5.	Image transfer to DCC-----	69
6.7.6.	Processing of CT Scans-----	69
6.7.6.1.	Image Quality Scrutiny-----	69
6.7.6.2.	Storing CT Scans-----	70
7.	STUDY ADMINISTRATION-----	72
7.1.	Organization Overview-----	72
7.1.1.	Department of Energy-----	73
7.1.2.	Study Chair-----	73
7.1.3.	Clinical Centers-----	73
7.1.4.	Data Coordinating Center-----	73
7.1.5.	Specimen Core Laboratory-----	73
7.1.6.	Genetics and Plasma Core Laboratory-----	74
7.2.	Committees-----	74
7.2.1.	Steering Committee-----	74
7.2.2.	External Protocol Review Committee-----	74
7.2.3.	Research Review Committee-----	74
7.3.	Web Pages-----	75
7.3.1.	Study Specific Web Page-----	75
7.3.2.	General Web Page-----	77
8.	POLICY MATTERS-----	79

- 8.1. Training and Certification----- 79
  - 8.1.1. BBB Training Sessions----- 79
  - 8.1.2. Consent Administration----- 79
  - 8.1.3. Internal Data Entry----- 79
  - 8.1.4. CT Technicians and Scanners----- 80
  - 8.1.5. Tissue and specimen collection technicians----- 80
  - 8.1.6. Questionnaire Administration----- 80
  - 8.1.7. Other Functions----- 80
- 8.2. Release of BBB Data or Specimens----- 80
- 8.3. Conflict of Interest Policy----- 81
  - 8.3.1. General Principles----- 81
  - 8.3.2. Individuals to be governed by these guidelines----- 82
- 9. REFERENCES----- 83

**BERYLLIUM BIO BANK (BBB)**

**PROTOCOL  
CHAPTER 1**

**TABLE OF CONTENTS**

	<b>Page</b>
1. INTRODUCTION-----	1
1.1 Summary-----	1
1.2 Purpose of the Study Protocol -----	2

## **CHAPTER 1**

### **INTRODUCTION**

#### **1.1 SUMMARY**

The Department of Energy (DOE) Beryllium BioBank (BBB) is being established to facilitate future beryllium disease research by collecting and archiving biological specimens and associated clinical data from individuals with (a) chronic beryllium disease (CBD), (b) beryllium sensitization (BES), and (c) beryllium exposure who are non-sensitized (BE-NS). The ultimate goal of this effort is to improve our understanding of beryllium-related health effects.

Participants will be recruited over a 36 month period from four participating clinical centers: National Jewish Health (NJH) Colorado School of Public Health, University of Colorado Anschutz Medical Campus (UCD); Hospital of the University of Pennsylvania (HUP), Philadelphia; University of California at San Francisco (UCSF), San Francisco; University of California at Los Angeles (UCLA), Los Angeles; and East Tennessee Pulmonary Group, Oak Ridge, Tennessee.

Following informed consent, specimens and data will be collected either at the time of clinical evaluation for diagnosis, or at the time of clinical follow-up for progression of disease. In some instances, participants may be invited to contribute already-available specimens and permit retrieval of clinical information from medical records. For the purpose of comparison, biological specimens and similar clinical data will be collected from BE-NS control subjects. All biological specimens and clinical data will be de-identified at the clinical centers before being banked and stored at the following locations: radiographic and clinical data will be stored at the Data Coordinating

Center (DCC) (UCD); biopsy tissue and lavage fluid and cells, and peripheral blood cell pellets at the Specimen Core Laboratory (SCL) (NJH); and blood specimens for DNA extraction and plasma to the Genetics and Plasma Core Laboratory (GPCL) (HUP). At the completion of the biobank collection period, specimens and data will be transferred to the National Jewish Health Biobank, which will maintain the biobank and, in collaboration with the Research Review Committee, manage inquiries and access for future investigators who have approved study proposals and are investigating the mechanisms and pathogenesis of BES and CBD.

## **1.2 PURPOSE OF THE STUDY PROTOCOL**

The Protocol for the BBB details the rationale, specifies the objectives, describes the design and organization of the study, and discusses patient recruitment, enrollment and protections. As the study progresses and the Protocol is updated and modified, the DCC will prepare and distribute (via postings to the Web page) revised versions as necessary. Protocol modifications will be announced by the distribution of a numbered memo to all key personnel at the Clinical Centers, Core Centers, DOE, and Institutional Review Boards. The memo will also be posted to the BBB Web page for future reference.



**BERYLLIUM BioBANK (BBB)**

**PROTOCOL  
CHAPTER 2**

**TABLE OF CONTENTS**

	<b>Page</b>
2. GOALS, BACKGROUND AND SIGNIFICANCE -----	4
2.1 Specific Goals -----	4
2.2 Background and Significance -----	5
2.3 Study Design -----	6

## CHAPTER 2

### GOALS, BACKGROUND AND SIGNIFICANCE

#### 2.1 SPECIFIC GOALS

The primary goal of the BBB is to enroll CBD, BES and BE-NS participants over 36 months to acquire biological specimens and clinical information to create a biobank of high scientific merit and utility for future investigation. To achieve this objective, the BBB will identify and recruit patients with CBD and BES who are scheduled to undergo medical evaluation for diagnostic purposes. Upon informed consent, participants will be asked to (1) donate blood to the biobank for DNA extraction, plasma and cell pellet; (2) complete a private interviewer-administered questionnaire to obtain demographic information, medical symptoms and history, smoking history, occupational and exposure history; (3) provide consent to review medical evaluation results and tests including physiologic and radiographic studies; (4) provide consent to review DOE exposure and work history records including years of employment, job titles, and building locations; and if appropriate; (5) provide permission to collect leftover bronchoalveolar lavage fluid, cells, and transbronchial biopsy lung tissue obtained for the purpose of a participant's clinical evaluation. In addition, if available, the BBB will accept leftover tissues specimens from autopsy, open lung biopsy, lymph nodes, and skin biopsy. The goal will be to enroll a wide spectrum of patients with respect to disease severity, progression, exposure, gender, age, and race/ethnicity. The BBB proposes to identify Be-NS controls who are frequency stratified to cases on the basis of DOE site, gender, race, ethnicity, age within decade, decade of hire based on enrollment of every 50 cases at all centers. Following IRB approval, BBB will send out letters to Current and

Former workers who have participated in medical surveillance. If interested in participation, the worker will return a contact card and his/her name will be stored until such time as sufficient controls are identified based on the enrolled cases criterion. Additionally, workers may demonstrate interest in participation by contacting BBB staff via telephone contact list on the BBB general website. We will screen 2 controls for every case to obtain frequency matched controls based on DOE site, gender, race, ethnicity, age within decade, decade of hire. At that time, the controls will be contacted and invited to enroll in the BBB. Staff will schedule an appointment at the closest Clinical Center or arrange for a telephone consent and interview, along with shipment of a blood collection kit to the participant or a local physician's office. The blood collection kit will contain complete instructions for drawing and shipping blood and all physicians' offices will be contacted prior to blood draw to ensure that blood will be drawn and shipped correctly. Specimens and clinical data from approximately equal numbers of CBD, BES and BE-NS participants should be collected.

## **2.2 BACKGROUND AND SIGNIFICANCE**

Chronic beryllium disease is predominantly an occupationally-acquired illness resulting from exposure to particulate, dust and/or fumes of beryllium products. In 1999 the DOE, in recognition of the adverse health effects associated with beryllium exposure, adopted its Beryllium Rule designed to provide medical monitoring programs for current and former DOE beryllium workers. As many as 70,000 DOE workers are estimated to have ever had beryllium exposure. Since initiation of these programs, approximately 45,000 blood Beryllium Lymphocyte Proliferation Tests (BeLPT) have been performed and approximately 1,000 cases of BES and 300 cases of CBD

identified (Stange 2004). Upon informed consent, specimens and data collected from these programs will become part of the BBB and serve as a resource for research on BES and CBD.

In the past 25 years, a great deal has been learned about the immunopathogenic mechanisms, genetic and exposure risk factors, and clinical features of BES and CBD. However there are many important, unanswered questions concerning these beryllium-related health conditions that can, in the future, be best addressed using a resource that has aggregated large numbers of cases and controls, and that has systematically collected and stored specimens and data on exposure and clinical -phenotypes in a well-characterized cohort.

### **2.3 STUDY DESIGN**

There will be three main sources of participants: (1) patients with BES undergoing initial or follow-up clinical evaluation to determine if they have CBD; (2) patients with CBD undergoing follow-up clinical evaluation to determine the extent of progression of disease; and (3) subjects who are beryllium exposed and involved in on-going medical surveillance to determine sensitization status. Standardized definitions of CBD, BES and BE-NS, and data to be collected are outlined in Chapter 4. The BBB will collect available specimens and clinical data, but will *not* require participants to undergo specific clinical tests. The purpose of collecting these data is to provide future investigators not only with needed biological specimens, but to allow them to best select cases and controls and to assess the relationships between clinical and exposure variables and results of assays performed on the biological specimens. In this way, researchers may, in the future, be able to not only

discover important features of disease pathogenesis, but also to relate those findings to clinically important consequences, such as disease severity, prognosis, and outcome. A power analysis indicates when we have 3 groups (control, sensitized, diseased) and the possibility of a protein or a dominant gene effect, if there is a baseline 5% incidence in the population, then with 500 individuals in each group, we will have an 80% power (with  $p = 0.05$ ) to detect an increase to 10% or a decrease to 2%. If the baseline incidence is 10%, then with 500 individuals within each group, we will have an 80% power (with  $p = 0.05$ ) to detect an increase to 16% and a decrease to 5.5%. We believe that this will give future researchers sufficient power to detect significant protein or genetic effects on beryllium sensitization or disease.

**BERYLLIUM BioBANK (BBB)**

**PROTOCOL  
CHAPTER 3**

**TABLE OF CONTENTS**

	<b>Page</b>
3. STUDY POPULATION AND PROTECTION OF HUMAN SUBJECTS--	9
3.1 Introduction -----	9
3.2 Eligibility Criteria -----	9
3.2.1 Inclusion Criteria-----	10
3.2.2 Exclusion Criteria-----	10
3.2.3 Case Definitions-----	10
3.3 Recruitment Strategies -----	12
3.4 Recruitment Goals -----	14
3.5 Informed Consent -----	15
3.6 HIPAA Compliance -----	17
3.7 Potential Risks-----	17
3.8 Data Safety Monitoring Plan and Adverse Events-----	21

**CHAPTER 3****BBB POPULATION AND PROTECTION OF HUMAN SUBJECTS****3.1 INTRODUCTION**

The BBB will facilitate future research by collecting biological specimens and clinical data for individuals with BES, CBD, and BE-NS. It is important that adequate numbers of individuals in each of these categories be enrolled. It is also important that individuals represent the full range of clinical phenotypes. To the full extent possible, individuals will be enrolled who meet specific diagnostic criteria, recognizing that in some instances individuals may vary in (a) the type, quality and quantity of information available, and (b) the precision with which they meet specific *a priori* diagnostic criteria. Adequate information will be obtained to allow future researchers to consider alternative diagnostic criteria when utilizing these biobank subjects' clinical data and specimens.

**3.2 ELIGIBILITY CRITERIA**

The biobank will collect specimens from current and former Department of Energy employees, contractors, and select vendors as listed below in Section 3.3. All patients who have undergone or who are undergoing medically indicated clinical evaluations will be potential candidates for specimen procurement as part of the BBB. Specifically, two major categories of health effects will be targeted for study, BES and CBD. A third group-- those with beryllium exposure but no evidence of immune sensitization to beryllium (BE-NS)--will provide control/comparison specimens for the two targeted groups. Minimum participation requirements include both a blood specimen and questionnaire response.

A BBB participant may not be enrolled more than once. The DCC will be able to link multiple samples from the same patient as necessary for analyses. It is recognized,

for example, that some individuals may undergo more than one clinical evaluation during the course of this biobank effort, that clinical data can be retrieved retrospectively from more than one clinical visit, and that individuals may change clinical status (e.g. from having BES without CBD, to developing CBD). In such circumstances, the longitudinal data will be captured under the same identification number.

### **3.2.1 Inclusion Criteria**

- a. 21 years of age or older.
- b. BES undergoing clinical evaluation for diagnostic purposes.
- c. CBD undergoing clinical evaluation to determine disease progression.
- d. History of past exposure to beryllium but who demonstrate no evidence of BES or CBD.

Because beryllium exposures in the workplace cause most cases of BES and CBD, these conditions occur almost exclusively in adults. As such, there is no expectation of recruiting children in this biobank.

### **3.2.2 Exclusion Criteria**

- a. Unable to provide informed consent,
- b. Unable to answer a questionnaire
- c. Unable to participate in a blood draw

### **3.2.3 Case Definitions**

For purposes of enrollment, the BBB has established diagnostic criteria. It is recognized that some individuals may meet some but not all of the “gold standard” diagnostic criteria, but that such individuals’ may be important to include in the biobank. Therefore, both “definitive” and “probable” diagnostic criteria for CBD are included.



a. Definitive CBD diagnostic criteria

The currently accepted criteria for the diagnosis of CBD rely on evidence of an immune response to beryllium (sensitization) and lung pathology. This is based on our current understanding of the pathophysiology of CBD as a delayed-type hypersensitivity response and the fact that the lung is the main organ affected by the disease.

Thus, the criteria for a **definitive diagnosis of CBD** will require the following: 1) immune response to beryllium, and 2) non-caseating granulomatous lung inflammation. The immune response to beryllium could be established by: 1) abnormal blood BeLPT, or 2) abnormal BAL BeLPT, or 3) positive skin patch test to beryllium.

b. Probable CBD diagnostic criteria

In individuals where a lung biopsy was not done or not possible, or in whom a biopsy was performed but due to collection methods may have yielded falsely negative results, a probable diagnosis of CBD can be made based on the presence of an immune response and radiographic or immune evidence of lung disease. Thus, a **probable diagnosis of CBD** will be based on: 1) demonstration of an immune response to beryllium along with either 2) radiologic abnormalities (on plain film or HRCT) consistent with granulomatous inflammation and sarcoid-like radiology including ground glass infiltrates, centrilobular nodules, or fibrosis, or 3) abnormal BAL BeLPT with BAL lymphocytosis. BAL lymphocytosis will not be used as a sole diagnostic criterion for CBD, as it can be caused by other common diseases like viral infections and asthma.

c. BES diagnostic criteria

Patients who have two positive blood or one positive BAL beryllium lymphocyte proliferation tests, but who have no lung pathology or radiographic evidence consistent with CBD, are considered to have beryllium sensitization without CBD. The currently accepted **definition for BES** requires (in the absence of lung pathology): 1) two abnormal blood BeLPTs or 2) one abnormal blood BeLPT and one borderline blood BeLPT or 3) one abnormal BAL BeLPT or 4) one positive skin patch test to beryllium.

d. BE-NS control subjects

Individuals occupationally-exposed to beryllium, who have at least one normal blood BeLPT and who have had no abnormal or borderline BeLPT's.

### **3.3 RECRUITMENT STRATEGIES**

To obtain the widest representation of patients undergoing clinical procedures, a multicenter approach will be utilized. This includes participation of:

- a. Pulmonary and occupational medicine physicians within each clinical center
- b. Pulmonologists and occupational medicine physicians providing care in geographic locations near a DOE site.

To obtain controls who most closely match the BeS/CBD cases, both current and former workers from all DOE and select DOE vendor sites will be invited to participate. Specifically, controls will receive a letter from the PI's explaining the BBB and inviting them to participate, and pamphlets as they participate in beryllium surveillance including:

- a. DOE former worker programs, including the National Supplemental Screening Program (NSSP)

- b. DOE onsite medical departments
- c. DOE vendors, including American Beryllium Company, Beryllium Corporation of America (Hazleton and Reading), and Speedring/Axsys Technologies.

In an effort to optimize specimen procurement and clinical data for phenotyping of participants, it is encouraged that a multidisciplinary team be involved in the BBB effort at each Clinical Center. This may include:

- a. A BBB Principal Investigator and co-investigators
- b. A dedicated BBB Clinical Coordinator
- c. Part-time administrative personnel or Clinical Coordinator to aid in scheduling of prospective participants, data collection and data/specimen transfer

Each Clinical Center will be responsible for developing a cohesive group of personnel to identify potential participants at their Clinical Center. All efforts should be made to recruit cases at the earliest time point in their clinical care as possible, as well as to recruit individuals who have been followed over time in the participating clinics. For those cases that have been followed longitudinally at the Clinical Centers, pre-selected clinical data from past evaluations will be captured if available. This will optimize the collection of adequate data for clinical phenotyping. BE-NS participants (controls) will be offered participation in the BBB as they are enrolled in Nssp, a DOE former worker program, or a vendor surveillance program. If they are interested in participating, they will contact the BBB for additional information and enrollment using either the e-mail address or phone number listed in the BBB general website, a BBB addressed, stamped information card, or on the brochure offered through the Nssp to

indicate they are interested in participation. Controls who consent to participate will do so by having their blood drawn either by their primary care physician, who will return the blood to the core laboratories in the postage paid, shipping packages supplied by the BBB, or by participating at a Clinical Center. The blood will be distributed to the core laboratories. The screening and recruitment processes will be the responsibility of the multidisciplinary team at each center following procedures set aside in this document. These efforts will be carried out while preserving the patient's privacy and confidentiality, in compliance with HIPAA and other governing requirements (45 CFR, Parts 160,164). Limited data will be collected on a screening log to monitor the recruitment process for each prospective enrollee and to determine whether the prospective participant has been previously enrolled. Uniform recruitment practices will be followed via use of this BBB protocol manual, the manual of operations (MOO), and centralized training of all clinical center staff.

Recruitment, screening, and enrollment will differ at each Clinical Center due to differences in staffing, infrastructure, patient catchment, and interdepartmental relations.

### **3.4 RECRUITMENT GOALS**

Clinical Centers will vary in their ability to recruit for this biobank. It is the expectation that varying numbers of participants will be recruited by each center. The initial goal will be to concentrate on recruiting subjects from three major categories of donors, including:

- a. Patients with CBD
- b. Patients with BES

- c. BE-NS subjects with known occupational exposure to beryllium without evidence of beryllium sensitization

As a general principle, the major goal of the BBB will be to maximize the number of participants with CBD or BES, but still to recruit sufficient numbers of BE-NS from the same facilities as the cases to permit future researchers to utilize them as controls.

### **3.5 INFORMED CONSENT**

Written informed consent of the subject will be obtained for all procedures and data collection prior to entry into the biobank protocol. Informed consent will be administered by authorized BBB personnel at each Clinical Center or by telephone who have obtained training in the ethical conduct of research. These individuals will receive training through the BBB to ensure uniformity of the consent process. Informed consent at clinical centers will take place in a private setting, such as a conference room or private office. Potential subjects will be allowed as much time as they require to make a thoughtful and reasoned decision. If the person desires, and in accordance with governing IRB requirements, he/she may take the informed consent information with them to discuss further with family and other advisors. If consent is to be obtained by telephone, the subject will contact the biobank coordinator who will then mail the consent to the subject and set up a specific time and date to go over each page of the consent. When finished, the subject will then mail the signed consent back to the biobank coordinator. Biobank personnel will thoroughly explain the BBB goals and procedures and answer any questions. The amount of time required for the interviews and procedures will also be explained. The BBB consent form will include check boxes

for the patient to decide if he/she consents to specific components of the biobank, including:

- a. Prospective collection of demographic and occupational history /exposure data and work history record. - **required**
- b. Prospective collection of blood sample -**required**
- c. Retrospective data review and retrieval of already existing biopsy specimens, clinical data from medical records, including pulmonary function tests and exercise test results, along with chest x-ray, and chest CT images for current patients.
- d. Prospective collection of both clinical data and biological specimens collected as a result of clinical evaluation for diagnosis/ follow-up of CBD
- e. Prospective collection of any leftover bronchoalveolar lavage fluid, cells and /or biopsy from a clinically indicated bronchoscopy or other biopsy procedure (i.e. specimens that will not be needed for any further clinical purposes).

Subjects will be reassured that they can still participate in the biobank if they choose to decline participation in certain aspects as outlined above. For example, an individual may decline to have their blood specimen used for genetic testing, but still be enrolled in the biobank having their blood drawn for other aspects of the protocol. Subjects will be informed that refusal to participate in any part of the BBB will not change their current or future care at the Clinical Center.

In order to remain in compliance with local governing Institutional Review Boards (IRB), each Clinical Center will customize the proposed standard consent form that will be developed by the Investigators and approved by the DOE Central Beryllium IRB.

Investigators at each Clinical Center will work with their IRB to develop an effective sampling and monitoring strategy to ensure that the approved procedures are being followed. The Clinical Centers will periodically monitor compliance and completeness of consent forms and report these findings to the Steering Committee.

### **3.6 HIPAA COMPLIANCE**

Each BBB Clinical Center will be responsible for its compliance with the current HIPAA requirements. This includes familiarity with data that are considered personal identifiers and should not be forwarded to DOE, the DCC or Core Laboratories. The DCC will design all BBB forms and databases to omit such variables. A participant information form will be kept at the Clinical Center in a secure location. This is the only identifying information that will be retained. It will be retained to allow the original Clinical Center to identify an individual should he/she decide to withdraw from the BBB. Additionally, each Clinical Center will fully explain its institution's HIPAA release form prior to obtaining the subject's consent. This form should include the DCC and the Core Laboratories as institutions that may review the subject's de-identified data.

### **3.7 POTENTIAL RISKS**

**Blood Draw:** Participants will be asked to donate 60 mls of blood to obtain genomic DNA, plasma, and a cell pellet. The blood draw is considered to be in the low risk category. Subjects may feel pain when the needle goes into the vein. A bruise may form at the site. There is a small risk of fainting. In about 1 in 10 cases a small amount of bleeding under the skin will produce a bruise. After subjects have given blood, they will be asked if they feel "light-headed", faint or ill in any way. If they do, they will be asked to stay for at least 10 minutes and will be served refreshments in order to raise

blood sugar and replenish fluids. Individuals will be allowed to lie down until their lightheadedness resolves. Equipment for checking vital signs, monitoring heart rhythm, and for performing cardiopulmonary resuscitation will be available.

**Questionnaire:** The questionnaire does not involve any physical risk. Questions will be restricted to demographics, medical symptoms and history, smoking history, and work and exposure history. If a study participant is uncomfortable with a question, he/she may choose not to answer

**Review of Clinical Data/Medical Records/Work Histories:** There is no physical risk involved in reviewing participant records.

**Collection of leftover specimens and tissue:** There is no physical risk involved in collecting leftover specimens and tissue.

**Coercive pressure:** It is possible that participants may feel pressured by their physicians to participate in the BBB. To avoid coercive pressure, our source population will receive a recruitment letter asking them to contact BBB personnel if they are interested in participating, and BBB visits will be held in a private location.

**Breach of privacy and confidentiality:** To avoid breach of privacy and confidentiality, BBB visits will be held in a private location. All data collected for the biobank will be de-identified. Subjects will not receive individual results, as no individual results will be obtained as part of this biobank, but instead will be obtained in future studies from the de-identified specimens.

**Insurability and employability:** Participants may have to disclose to insurance companies or future employers that they participated in studies involving genetic research. To protect participants from genetic discrimination, individual genetic results



will not be available and will not be obtained as part of the biobank. The BBB will store only de-identified specimens and clinical data for future research. The BBB itself will not conduct research.

**Risk/Benefit Analysis:** The risks associated with the BBB are considered minimal. The biobank procedures include a low volume blood draw, which has low physical risk. There is no physical risk to participants for completing a questionnaire, having their records reviewed, or collecting leftover specimens and tissue. While the potential for non-physical harms exist because participants are a vulnerable population and will be donating blood for genetic research, the risk is low because individual genetic study results will not be available. The BBB will store only de-identified specimens and clinical data for future research.

While most participants receive no direct benefit, future studies for a better understanding of disease may lead to many benefits. (1) Knowledge will increase our understanding of the disease; (2) Identifying a protective level of beryllium exposure could lead to preventing disease among future workers; (3) Understanding the genetic mechanisms of the disease may promote the development of more effective diagnostic tools and treatment; (4) Knowing why some people with BES and CBD get sicker than others may provide insight in providing treatment. An excess morbidity and more importantly mortality compared to the general population has been identified for CBD. Patients benefit from earlier recognition, more aggressive approach to defining the stage of disease, and better management of the disease. In addition, a better understanding of the pathogenesis, diagnosis, treatment and primary prevention will be

a benefit to society in general. Thus, the risk of participation is small and justified by both the personal and societal benefits.

**Privacy/Confidentiality Protections:** The BBB and Clinical Centers will obtain a Certificate of Confidentiality, issued by the NIH under the Public Health Service Act (41 U.S.C. 241(d) to protect the principal investigators of this biobank as well as the Clinical Centers from having to release personal identifying information about participants. Participants' personal identifying information will be protected from civil, criminal, administrative and legislative proceedings at the federal, state, and local levels. The Certificate will remain in effect until the biobank is completed. Protection of biobank participants' personal identifying information is permanent.

To protect personal privacy and maintain confidentiality, subjects will be assigned unique biobank identification numbers by the DCC, which bear no identifying information. The Clinical Centers will remove all personal identifying information from specimens and data before being banked and stored at See the Manual of Operations (MOO) for standard protocol to remove personal identifying information.

**Genetic Research:** It is likely that genotyping may be performed by future researchers using specimens from this biobank. Such genetic testing will be for the purpose of research only and is not considered a standard medical test. The biobank itself will perform no genotyping. The purposes of future genetic research using the biobank specimens will be to study the mechanism of disease interaction with exposures and not to assess individual disease risk from a clinical standpoint.

Because the specimens will only be provided for future studies utilizing de-identification, individual genetic research results will not be available. The BBB will store only de-identified specimens and clinical data for future studies.

### **3.8 DATA SAFETY MONITORING AND ADVERSE EVENTS:**

Each Clinical Center, with assistance from the DCC, will be responsible for monitoring and reporting on protocol adherence. Four areas will be monitored:

- (a) Meeting inclusion/exclusion criteria
- (b) Informed consent
- (c) Study withdrawal
- (d) Project progress

Problems with biobank-related procedures will be reported to the principal investigators at each Clinical Center site by the phlebotomists, biobank participants, or BBB personnel.

**Adverse Events:** Reporting of adverse events, morbidity, mortality, or unexpected events will be done in accordance with the CBeIRB and each Clinical Center's IRB. In addition, if it comes to the attention of the Clinical Center staff that an adverse event is definitively related to a BBB procedure, even if it is outside a reporting window, Clinical Center BBB personnel will report the event to the relevant IRBs.

This protocol calls for participants to complete venipuncture, a questionnaire, and to permit Clinical Centers to access to their clinical data and stored specimens. With the exception of the questionnaire and venipuncture, adverse events (AE) or serious adverse events (SAE) related to clinical procedures would not be considered to be a consequence of research, as they are not being performed for research purposes.

Adverse events may occur as a result of venipuncture. Serious adverse events due to venipuncture are rare. A serious event is defined as an event that

- A. causes death
- B. is life-threatening
- C. results in hospitalization or prolongs a hospitalization
- D. results in a serious or persistent disability
- E. represents a serious hazard or could cause serious harm to the research participant.

**BERYLLIUM BIO BANK (BBB)****PROTOCOL  
CHAPTER 4****TABLE OF CONTENTS**

	<b>Page</b>
4. CLINICAL CENTER PROCEDURES -----	24
4.1 Overview -----	24
4.2 Interviews and Questionnaires -----	25
4.2.1 Medical and Family History-----	25
4.2.2 Exposure History-----	25
4.3 Biological Specimen Collection-----	26
4.3.1 Overview of biological specimen collection-----	26
4.3.2 Role of the Specimen Core Laboratory (SCL)-----	27
4.3.3 Overview of tissue specimen acquisition-----	28
4.3.4 Acquisition of fixed tissue specimens-----	28
4.3.5 Tissue labeling and supplemental information-----	28
4.3.6 SCL reference slides-----	29
4.3.7 Blood specimen acquisition-----	29
4.3.8 Bronchoalveolar lavage fluid and cell specimen acquisition---	30
4.4 Imaging Studies-----	30
4.4.1 Computed Tomography (CT) Scans-----	30
4.5 Medical Record Data Abstraction-----	31
4.5.1 Pathology reports-----	33
4.5.2 Radiology interpretations-----	33
4.5.3 Pulmonary Function Tests-----	34
4.5.4 Lung Volume measurements-----	34
4.5.5 Exercise tests-----	35
4.5.6 Arterial blood gas-----	37
4.5.7 Diffusing capacity for carbon monoxide (DLCO)-----	37
4.5.8 Clinical laboratory data-----	38
4.6 Data Entry-----	38

## CHAPTER 4

### CLINICAL CENTER PROCEDURES

#### 4.1 OVERVIEW

Collection of diagnostic data will include retrieving and recording of relevant medical and exposure history, imaging data, and pulmonary physiological and lung function testing as defined below. Blood specimens will be obtained for plasma, DNA extraction and blood cell pellet and storage of these specimens for later investigative purposes. An interview-administered questionnaire will be obtained and include clinical questions to determine the extent of symptoms, associated medical illnesses, medications, smoking habits, environmental exposure, and quality of life; and detailed occupational exposure questions including years of employment, job titles, and building locations. Thus, questionnaire administration and venipuncture are the only biobank-specific procedures to which participants are asked to consent. All other biological specimens and clinical material will be obtained post-hoc from past clinical procedures and medical record review. The primary goal of the BBB is to collect biological specimens for future study. However, biological specimens without clinical or exposure data are of limited value, which makes the collection of clinical and exposure data an important companion goal for the BBB.

When available, the medical record will be reviewed to: 1) determine the eligibility of the patient to participate in the BBB; 2) collect information concerning previous imaging studies (chest x-ray, CT scans) that were performed that may be used as data for the BBB; 3) collect qualifying pulmonary function test and other physiologic data that may be used as data for the BBB; and 4) gain other information that may assist or

otherwise supplement the data collection that will primarily be carried out by interviewer-administered questionnaires and collect BBB protocol-related procedures. The medical record will only be used to collect information and clinical data that is relevant to the collection of the information listed in the study forms.

## **4.2 INTERVIEWS AND QUESTIONNAIRES**

### **4.2.1 Medical and Family History**

A limited medical history will be obtained at the time of the participant's study visit. This will include data on the enrollee's medical history and family history in first-degree relatives with chronic lung disease. The biobank will collect data that will allow future investigators to determine the onset and progression of beryllium-disease associated symptoms, e.g. shortness of breath, dyspnea on exertion, cough and sputum production, night sweats and fatigue. Because of its potential relevance to phenotyping and to mechanism of disease, the BBB will also collect information on medical treatment, medication usage, and other medical conditions that may interact or confound interpretation of clinical data regarding CBD, BES, or BE-NS.

### **4.2.2 Exposure History**

Exposure history will include determination of smoking status and extent of exposure to tobacco smoke. Occupational exposure to beryllium, including years worked with beryllium, beryllium job title and industry will be recorded- Additional information about other potentially important occupational exposures will be recorded. BBB will also obtain relevant history for exposure to pharmaceuticals and radiation known to induce pulmonary fibrosis. These data will be obtained by a patient interview.

## **4.3 BIOLOGICAL SPECIMEN COLLECTION**

### **4.3.1 Overview of biological specimen collection**

Pathology specimens, referred to here as “tissue,” are considered a particularly important, albeit limited, resource for future research. Other biological specimens are also important and limited resources. This section addresses specific issues of tissue and other biological specimen acquisition and storage, first emphasizing tissue.

With regard to tissue, the BBB will request that only those tissues be sent that will not be needed by the local pathologist for purposes of clinical diagnosis. It is likely that these specimens will mainly be available from participants with CBD, BES, and in some cases from individuals who had abnormal imaging studies who are BE-NS and underwent biopsy to determine alternative causes of lung disease. Furthermore, it is anticipated that these specimens will be shipped at a date after the local clinical pathologists have made their final determinations of the clinical pathology diagnosis.

Most tissue will be obtained from the lung, mainly by transbronchial biopsy, but in some instances by video-assisted thoracoscopy or open lung biopsy. It is recognized that under certain circumstances, participants with CBD, BES, or BE-NS may undergo procedures that may result in acquisition of additional types of tissue specimens, in addition to lung tissue, including thoracic lymph nodes, skin, liver or other organs. Autopsy tissue will be accepted from individuals who fulfill minimum requirements of at least one year full-time employment with the DOE and a previous demonstration of beryllium sensitization. The biobank, while focusing principally on the acquisition of available lung specimens, will accept tissue from other organs, as described in the Manual of Operations (MOO). Tissue only specimens will be “enrolled” by a single



Clinical Center.

#### **4.3.2 Role of the Specimen Core Laboratory**

The BBB Specimen Core Laboratory (SCL), based at National Jewish Health, will collect and store specimens of lung including BAL fluid and cells, and other biological materials. This will include tissue that may have been obtained in order to determine if a participant has the diagnosis of CBD, resulting primarily from transbronchial biopsy, from participants with CBD, BES and in some cases BE-NS. Tissue collection is one of several component activities of the National Jewish Health Specimen Core Lab. Other biological specimens to be collected and stored at the SCL are described below, including BAL fluid and cells, and peripheral blood cell pellets. DNA and plasma will be processed at the Genetics and Plasma Core Laboratory (GPCL) at Hospital of University of Pennsylvania, as described below.

The role of the SCL is to:

- 1) Collect, process and store biological specimens sent to the SCL from the BBB Clinical Centers and
- 2) Transfer the specimens based on DOE/DCC approval
- 3) Maintain records, regarding the number, volume, quality and location of all specimens collected and stored.

#### **4.3.3 Overview of Tissue Specimen Acquisition**

Tissue pertinent to the diagnosis of CBD will be collected by each Clinical Center for storage at the SCL, which will then transfer to the National Jewish Health BioBank for distribution for future research. The BBB will request that Clinical Centers obtain only those tissues not used by the local pathologist for diagnosis.

There will be two clinical situations in which there is potential for tissue to be collected by the Centers. These will include:

1. **Prospective Biopsy:** The participant is enrolled in the BBB and the participant's physician will take a biopsy of tissue as part of a diagnostic evaluation.
2. **Retrospective Biopsy:** The participant is enrolled in the BBB and the participant's physician will send in previously biopsied specimens relevant to the diagnosis of BeS or CBD.

#### **4.3.4 Acquisition of Fixed Tissue Specimens**

All fixed tissues that are obtained prospectively by biopsy, or other tissue resection and that are approved for admission to the biobank should be prepared according to the instructions given in the BBB Manual of Operations (MOO).

All Clinical Centers will insure that tissue specimens can be released by their clinical pathology department, i.e. that the determination of clinical diagnosis has been made, prior to specimen transfer to the biobank.

#### **4.3.5 Tissue Labeling and Supplemental Information**

Clinical sites will be responsible for properly labeling specimens sent to the SCL, in accordance with the MOO. In addition, they will complete a data form that describes the specimen(s).

The individual specimen containers or blocks will be pre-labeled with the tissue identifier (previously supplied by DCC). A matching tissue identifier will be recorded on the data form, along with information such as the type of fixative/preservation method, and the lobe or organ from which the specimen was taken.

#### **4.3.6 SCL Reference Slides**

The SCL will make an H & E diagnostic reference slide from a fixed, paraffin-embedded slide specimen for each biopsy that is obtained from the participant.

#### **4.3.7 Blood specimen acquisition**

Participants will be requested to undergo venipuncture at the time of enrollment, after completion of informed consent. Participants will elect to have blood drawn for up to three purposes: 1) banking of plasma, 2) banking of cell pellet for future studies of mechanisms of disease (non-genetic research), 3) extraction and banking of DNA for future genetic research. Depending upon the choice of the participant, varying amounts of blood may be obtained, up to a maximum of 60 ml (eg. for the individual who agrees to have blood stored for all three purposes).

The Clinical Centers will obtain and send peripheral blood samples, in appropriate tubes and volumes, as specified in the MOO to one or two sites: 1) SCL for cell pellet, 2) GPCL for DNA extraction and plasma. For plasma and DNA, up to 30 ml may be obtained. For cell pellet, 30 ml will be obtained.

The Clinical Centers will be responsible for labeling and storing these samples under the appropriate conditions until shipment to the SCL and GPCL. Refer to the Manual of Operations for these procedures.

#### **4.3.8 Bronchoalveolar lavage fluid and cell specimen acquisition**

Participants who have undergone bronchoscopy with bronchoalveolar lavage may elect to permit the BBB to store leftover specimens, including leftover bronchoalveolar lavage fluid (BALF) and bronchoalveolar lavage cells. The BBB will not request participants to undergo BAL, but will only request permission to use leftover

specimens from clinical procedures.

The Clinical Centers will retrieve leftover BALF and BAL cell specimens, in appropriate tubes and volumes, as specified in the MOO, and forward to the SCL for storage. It is recognized that in most cases, BALF will be available, but that BAL cells often will not be available.

The Clinical Centers will be responsible for labeling and storing these samples under the appropriate conditions until shipment to the SCL. Refer to the Manual of Operations for these procedures.

#### **4.4 IMAGING STUDIES**

##### **4.4.1 Computed Tomography (CT) Scans**

The goal for the BBB imaging component is to collect available CT scan data on greater than 80% of the recruited BBB participants. The participant must consent to their clinical scans being stored (anonymously) in the biobank for future research purposes, and consent to the sharing of results and anonymized image data with future researchers. It is the responsibility of the Clinical Centers, with assistance from their radiology departments, to obtain copies of CT scans in DICOM format on CD-ROM and to transmit these to the DCC for storage in appropriate format specified in the MOO.

It is recognized that there may be a variety of protocols that have been used to obtain CT scans on participants at their various Clinical Centers. While standardization is desirable, the protocol does not call for participants to undergo this procedure; only to obtain the CT images that were obtained for purposes of clinical evaluation. Thus, it is likely that digital images may vary by center. CT data will be accompanied by data

indicating what equipment and CT protocols were employed by the center's radiology department. Future researchers may then determine the suitability and types of CT data that they choose to utilize in their analyses. It is beyond the scope of this biobank to collect all raw data from CT, but rather to capture the generated images from these clinical studies in appropriate DICOM format. It is anticipated that the participants who have undergone CT will have CT scan images of one or more of the following major types:

1. High-Resolution CT of the chest with non-contiguous axial images obtained in full inspiration.
2. Full Three-Phase CT of the chest with contiguous images (see MOO).

CT scans that are available will be collected from 1) time of first evaluation, 2) time of an evaluation at which diagnosis changes (eg. beryllium sensitization progresses to chronic beryllium disease), 3) time of any evaluation at which the treatment has changed, and (4) at the time of current evaluation, as specified in the MOO

#### **4.5 MEDICAL RECORD DATA ABSTRACTION**

Clinical Centers will be responsible for retrieving and reviewing medical records and for abstracting data from them for inclusion in the biobank database. The purpose is to enable future investigators to analyze their results in the context of information regarding a participant's clinical phenotype; and to aid investigators in the future who may want to analyze data or design studies based on certain clinical or demographic characteristics.

It is expected that the volume, time line, quality and completeness of medical

data retrieved from records will vary widely, In recognition of these limitations, the protocol calls for specific time points of data to be included whenever possible. These are to include data from 1) time of first clinical evaluation; 2) time at which an individual was identified as having changed clinical category (eg. progressed from BES to CBD); and 3) time at which major clinical intervention was required (eg. initiation of treatment; major modification in treatment), as detailed in the MOO, and (4) time of current evaluation.

The retrieved medical record (de-identified) information will include the following categories of data: 1) Pathology reports, 2) Radiology interpretations of CT scans and chest x-rays (including International Labor Organization (ILO) B-readings), 3) pulmonary function test results, including diffusing capacity for carbon monoxide (DLCO), 4) exercise testing results, 5) arterial blood gas analysis results, and 6) clinical laboratory data from prior blood and BAL tests. As described in the MOO, these data will be abstracted to appropriate data collection forms for entry by the Clinical Centers into a web-enabled data system maintained by the DCC, in a manner that is in compliance with instructions regarding the de-identification of clinical information.

In the section below, general guidelines for the type and quality of data to be obtained is described, recognizing that clinical centers will not necessarily conduct all clinical tests in identical fashion. Sufficient additional information (e.g. equipment used, normal ranges for laboratory tests, etc.) will be obtained to allow future investigators to make the most effective use of the clinical phenotyping data set.

#### **4.5.1 Pathology reports**

De-identified pathology reports and a pathology data abstraction form that

captures key descriptors included in the interpretation of the specimen findings by the clinical pathologist will be submitted to the DCC. These reports will match any tissue specimens submitted to the biobank. Even if tissue specimens are unavailable for submission to the SCL, any pathology reports that were relied upon for clinical diagnosis and that are needed by the biobank to make the determination of whether an individual meets study diagnostic criteria will be provided to the biobank and included in data collection. The MOO outlines the process for de-identification and for the entry of pathology reports and the abstracted key descriptors into the database.

#### **4.5.2 Radiology interpretations**

De-identified radiology reports will be submitted to the DCC for both the CT scans and chest x-rays that are to be included in the database and those available from prior time points as outlined above. Clinical Centers will provide copies of radiology interpretations that have been stripped of identifiers, and will also complete a radiology report data abstraction form for the CT scans. In the case of chest x-rays, clinical radiology reports and a chest x-ray data abstraction forms will be submitted. Whenever available, International Labor Organization (ILO) B-reader reports will also be submitted to the DCC. It is estimated that the majority of participants will already have B-readings available. The biobank will not collect actual chest x-rays and will not perform de novo B-readings.

#### **4.5.3 Pulmonary Function Tests**

##### **Spirometry**

Spirometry is a valid, reproducible means of monitoring the severity and the change in the severity of the respiratory component in lung disease. Spirometry is the timed-based measurement of the amount of air that can be forcefully exhaled from the lungs after a full inspiration. In the BBB, we will record the measurement of the forced expiratory vital capacity (FVC), the Forced Expiratory Volume at 1 second of expiration (FEV1) and the ratio of these two measures (FEV1/FVC). Spirometry included in the database must have been performed in a standardized manner in accordance with American Thoracic Society (ATS) guidelines, as described in the BBB MOO, and must meet quality control requirements described in that document. Principal Investigators at the Clinical Centers will review all spirometry for acceptability prior to data transmission to the BBB.

#### **4.5.4 Lung Volume Measurements**

While spirometry measures the amount and rate of air flow exhaled from the lungs it is not an accurate measure of the total lung capacity which depends not only on the vital capacity (VC), the total air which is exhaled, but also on the residual volume (RV) which measures the amount of air remaining in the lungs at the end of a full expiration. Another measure, functional residual capacity (FRC) is a measure reflecting the air remaining in the lung at the end of a normal tidal breath; Usually FRC also represents the volume at which the inward recoil of the lungs is balanced by the outward recoil of the chest wall. In restrictive lung diseases such as advanced CBD, the TLC, RV and FRC (TGV) are symmetrically decreased. In early CBD, airflow obstruction can be observed, and later in the disease course, a mixed pattern of obstruction and restriction may be seen. When obstruction is present, these parameters



may increase with the RV being disproportionately increased compared to the TLC. The BBB will retrieve from medical records body plethysmographic lung volume data that was obtained at the designated clinical time points, as outlined above and detailed in the MOO.

#### **4.5.5 Exercise Tests**

It is anticipated that the majority of CBD and BES, as well as some BE-NS participants will have undergone one of two forms of exercise testing at the time points sought: six minute walk or cardiopulmonary exercise test. Given that there will have been differences in the ways in which past tests were conducted at the different Clinical Centers, efforts will be made to not only capture key data from these studies but to also record the equipment and methods used, oxygen concentration and altitude at which the study was completed, to enable future researchers to optimize their use of the data. Whenever possible, cardiopulmonary exercise test data will be included, (preferentially over six-minute walk test data).

##### **1) Six-Minute Walk Test**

The six-minute walk test is a timed walk involving a familiar activity and requiring minimal technical resources. It has been shown to be a reproducible objective indicator of functional performance. However, unlike cardiopulmonary exercise testing, it does not allow collection of basic physiologic data that may be useful in determining mechanisms of change or patient selection. It is important to emphasize that this is a test of maximum exercise performance. Data retrieved regarding this test must be obtained from studies that were determined to have followed the recommendations of the American Thoracic Society (ATS) Statement for this test procedure. The information

to be extracted will include distance walked and pulse oximetry and/or arterial blood gas measurements obtained at rest and exercise.

## **2) Cardiopulmonary Exercise Test**

Cardiopulmonary exercise (CPX) testing measures the integrated response of the pulmonary mechanics, gas exchange, cardiovascular, and peripheral muscle systems. (REF: Pappas). Known and yet undeclared hypotheses utilizing this testing may relate to the functional impact of the disease process, determination of associations between lung tissue characteristics and the phenotypes of systemic processes occurring parallel to the pulmonary process, or in series either preceding or consequent to the pulmonary pathology. In addition, assessment of exercise gas exchange parameters associated with tissue and computed tomography parameters may provide insights into molecular-cellular-anatomic-physiologic translational relationships.

There will be two major types of testing to be included in the data base: Type I – Symptom limited cycle ergometry CPX without serial arterial blood gas (ABG) sampling, and Type II – CPX with serial ABG sampling at rest, unloaded and maximal exertion. Clinical Center physicians determine the type of test performed, because they are done for purposes of clinical assessment, not solely for biobank purposes. Efforts will be made to standardize the clinical testing protocols among the BBB Clinical Centers prospectively.

Details on the personnel certification, equipment and CPX procedure, data to be abstracted, are given in the BBB MOO.

### **4.5.6 Arterial Blood Gas**

Arterial blood gas (ABG) analysis is used to measure other data elements that can be used to classify the severity and the progression of lung disease, especially CBD. Abnormalities in ABG are among the earliest changes described in CBD. Arterial blood is collected to determine the partial pressures of CO<sub>2</sub>, O<sub>2</sub> and the pH of the blood and to calculate the alveolar-arterial gradient (A-a gradient). Data to be abstracted is summarized in the MOO and on data capture forms, and will include direct measures as well as calculated A-a gradient, altitude, supplemental oxygen use at time of testing, and other variables necessary to interpret results. These physical measures will aid investigators in creating clinical phenotypes for the participant. .

#### **4.5.7 Diffusing Capacity for Carbon Monoxide (DLCO)**

The DLCO test can be used to detect early stages of diffuse lung disease even when more standard tests such as spirometry and chest X-rays may appear normal. In particular, the DLCO test will measure the lung's ability to perform gas exchange. This is done by measuring the amount of carbon monoxide that can be absorbed by the lungs for a specific time interval (usually ten seconds). The inability of the lungs to perform gas exchange is helpful in staging the severity and progression of CBD. There are two major methods of performing DLCO measurements, clinically, as described in the MOO. Data abstraction forms will be used to capture both the results and methods used for determining DLCO.

#### **4.5.8 Clinical Laboratory Data**

A limited set of clinical laboratory data will be abstracted from medical

records at the same time points described above and in the MOO. The data to be retrieved and entered into the database will serve the following purposes: 1) to determine enrollment eligibility (e.g. results of blood BeLPTs), 2) optimally interpret mechanistic data (e.g. white blood cell count and differential), and/or 3) contribute to the assessment of clinical phenotype by severity, progression, or state of inflammatory response (e.g. BAL cell count and differential). The BBB will not perform venipuncture for the purpose of performing clinical laboratory tests. For example, no new blood BeLPTs will be obtained for the biobank. The BBB will rely on the available clinical laboratory data. The clinical laboratory test data that will be retrieved will include a limited subset of the available clinical lab results, as detailed in the MOO and data retrieval forms. All available blood and BAL Beryllium Lymphocyte Proliferation Test (BELPT) results from clinical testing will be recorded, along with data needed to interpret the results (e.g. cut-off value for positive test, laboratory, calculation method, etc.). Coordinators will record the results of mycobacterial and fungal stains and/or cultures performed on lavage to exclude any infectious process that may affect the lung.

#### **4.6 DATA ENTRY**

Data retrieval forms will be completed for all clinical data abstracted from medical records to minimize errors before data entry into the IDMS. If a form is incomplete either because the test was not performed or clinical report was not available, the clinical coordinator will indicate so on the specific form. The PI and coordinator are responsible for completeness and accuracy. Signatures of coordinators and PIs (if required) are necessary on every form. After entry into the IDMS, hard copies of forms

will be retained in the participant's file. Completed forms and entry into the IDMS for the current (BBB) visit will be completed no later than 8 weeks after a participant has been enrolled.

**BERYLLIUM BIOBANK (BBB)**

**PROTOCOL  
CHAPTER 5**

**TABLE OF CONTENTS**

	<b>Page</b>
5. CORE LABORATORY PROCEDURES-----	41
5.1 Overview of Cores-----	41
5.2 Specimen Collection and Processing Center (SCP)-----	41
5.2.1 Shipment and Tracking of Samples -----	41
5.2.2 Specimen Collection and Processing -----	42
5.2.3 Tracking receipt of specimens -----	42
5.2.4 Processing of specimens-----	43
5.2.5 Storing of blood specimens-----	43
5.2.6 Redistribution of specimens-----	44
5.3 Genetics and Plasma Core Laboratory (GPCL)-----	44
5.3.1 Shipment and Tracking of Data -----	45
5.3.2 Specimen Collection and Processing-----	45
5.3.3 Tracking receipt of specimens -----	45
5.3.4 Processing of specimens-----	46
5.3.5 Storing of DNA specimens-----	46
5.3.6 Redistribution of DNA and plasma specimens-----	46

## CHAPTER 5

### CORE LABORATORY PROCEDURES

#### 5.1 OVERVIEW OF CORES

To manage the biobank in the most efficient and consistent manner, the BBB will consist of Clinical Centers for enrollment and acquisition of specimens and data and two Core Laboratories: the Specimen Core Laboratory (SCL) and Genetics and Plasma Core Laboratory (GPCL). The SCL, based at National Jewish Health, will serve as the interim biobank for all specimens until the end of the collection period when samples will be transferred to the NJH Biobank. Blood for DNA extraction and plasma will be shipped and interim-stored at Hospital of the University of Pennsylvania. Both laboratories will work integrally with the Data Coordinating Center (DCC) at Colorado School of Public Health, University of Colorado Anschutz Medical Campus, discussed below.

#### 5.2 SPECIMEN CORE LABORATORY (SCL)

##### 5.2.1 Shipment and Tracking of Samples

The following materials will be collected at the BBB Clinical Centers and shipped to the SCL/GPCL (see Chapter 4):

- Peripheral blood (DNA, plasma, cell)
- **If available from clinical procedures:** Lung and other biopsy tissue specimens including BALF fluid and cells

All specimens will be stored under appropriate conditions as detailed in the MOO, until shipment to the core laboratories.

Specimens will be obtained at the clinical center in appropriate collection tubes or transfer containers as outlined below and shipped in pre-supplied polyfoam shipper boxes, as detailed in the MOO on day one of three consecutive business days with no intervening holidays (e.g. tissues can be shipped on Monday through Wednesday assuming no holiday interference). This is to allow for unforeseen shipping and receiving problems. Most of the materials for shipping are included in the shipping kit.

Tissue specimens will be retained in the biobank at the National Jewish Health in Denver under the supervision of the study pathologist.

### **5.2.2 Specimen Collection and Processing**

The SCL will be responsible for the following:

- Tracking and logging receipt of specimens from Clinical Centers
- Separating blood cells from peripheral blood, aliquoting and cryopreserving blood cell pellets.
- Hematoxylin and eosin staining of representative tissue block sections
- Processing of bronchoalveolar lavage fluid and cells, including aliquoting of specimens and cryopreserving cells.
- Logging specimen-specific data in BBB central database
- Short term storage of specimens (See 5.2.6)
- Transfer of samples to the NJH BioBank, the BBB's long term storage facility (See 5.2.6)

The details of these procedures are provided in the MOO.



### **5.2.3 Tracking receipt of specimens**

Specimens will be shipped on Monday through Wednesday only. Step by step instructions for blood shipments are detailed in the Manual of Operations. Clinical centers will notify the SCL that specimens are being shipped, prior to shipping. All specimens will be shipped by next day priority delivery. The SCL will inform centers of any problems that may have arisen in the handling, labeling or shipping process and also notify the DCC for purposes of quality control and quality improvement. Specimens will be logged into a central database, in order to identify the date of receipt, condition, type, number and volume of specimens, keyed to participant ID.

### **5.2.4 Processing of Specimens**

Once received at the SCL, specimens will be processed, aliquoted, and stored in accordance with the MOO. The major activities of the SCL with regard to specimen processing will include separation of blood cells and aliquoting and cryopreservation of pellets, according to MOO requirements. Processing and aliquoting BALF specimens, aliquoting and cryopreserving BAL cell pellets, and transferring pathology specimens to the biobank pathologist Dr. Carlene Cool, for preparation of tissue sections and block storage. The SCL will then log details regarding the number, volume, and type of specimen to be stored or to be transferred to the pathologist.

### **5.2.5 Storing of Blood Specimens**

All pathology tissue and biological specimens will be stored in the SCL or with Dr. Cool at National Jewish in the proper storage facilities, 4°C, -20°C, or -80°C or liquid nitrogen, depending on the specimen requirements. All freezers/refrigerators are

backed up with an alternate electrical source to prevent warming the specimens in the case that the main electrical source at the SCL is interrupted.

Table 5.2 summarizes the storage conditions at the SCL for each specimen type.

**TABLE 5.2**  
**Archival Storage Conditions**

Paraffin blocks	Room temperature
Slides	-20°C or -80°C
Blood - plasma	-80°C
BALF	-80°C
Blood cell pellet	liquid nitrogen
BAL cell pellet	Liquid nitrogen

### 5.2.6 Redistribution of specimens

The SCL will retain all specimens until the end of the collection period. Once all samples have been processed and logged, they will be transferred to the NJH Biobank, located at National Jewish Health. The NJH Biobank will have no working relationship with the SCL once samples have been officially transferred. The NJH Biobank will work directly with the DCC to ensure that samples requested by researchers will be adequately fulfilled. For further details regarding the application and distribution of samples, please see the Specimen Request Protocol and/or the BBB Tissue Distribution Process.

### **5.3 Genetics and Plasma Core Laboratory (GPCL)**

The GPCL at the Hospital of the University of Pennsylvania will receive blood specimens directly from the Clinical Centers. It is expected that these will be shipped at the same time that blood specimens are being shipped to the SCL (see previous section).

#### **5.3.1 Shipment and Tracking of Samples**

The following materials will be collected at the BBB Clinical Centers and shipped to the GPCL (see Chapter 4):

- Peripheral blood for DNA extraction and plasma separation

All specimens will be stored under appropriate conditions as detailed in the MOO, until shipment to the GPCL.

Specimens will be shipped to the GPCL in pre-supplied polyfoam shipper boxes, as detailed in the MOO on day one of three consecutive business days with no intervening holidays (e.g. tissues can be shipped on Monday through Wednesday assuming no holiday interference). This is to allow for unforeseen shipping and receiving problems. Most of the materials for shipping are included in the shipping kit.

#### **5.3.2 Specimen Collection and Processing**

The GPCL will be responsible for the following:

- Tracking and logging receipt of specimens from Clinical Centers
- DNA isolation and plasma separation from blood
- DNA and plasma quality assurance
- Aliquoting of DNA and plasma

- Logging specimen-specific data in BBB central database
- Short term sample storage
- Redistribution of samples to NJH long term storage facility

The details of these procedures are provided in the MOO.

### **5.3.3 Tracking receipt of specimens**

All specimens will be shipped with labels that uniquely identify the participant.. Specimens will be shipped on Monday through Wednesday only. Step by step instructions for blood shipments are detailed in the Manual of Operations. Clinical centers will notify the GPCL that specimens are being shipped, prior to shipping. All specimens will be shipped by next day priority delivery. Upon receipt, the GPCL will log in all specimens on the date that they have been received. The GPCL will inform centers of any problems that may have arisen in the handling, labeling or shipping process and also notify the DCC for purposes of quality control and quality improvement. Specimens will be logged into a central data base, in order to identify the date of receipt, condition, number and volume of specimens, keyed to participant ID.

### **5.3.4 Processing of Specimens**

Once received at the GPCL, blood specimens will undergo the DNA extraction and plasma separation as detailed in the MOO, be checked for DNA purity and quantity, aliquoted, and stored in accordance with the MOO.

### **5.3.5 Storing of DNA Specimens**

All DNA specimens will be stored in the GPCL at HUP in proper storage facilities. All freezers are backed up with an alternate electrical source to prevent warming the specimens in the case that the main electrical source at the GPCL is interrupted.

### **5.3.6 Redistribution of DNA and plasma specimens**

The GPCL will retain all aliquoted DNA specimens until instructed by the funding agency and steering committee to transfer specimens to the central biobank to be provided by NJH.

## BERYLLIUM BIOBANK (BBB)

### CHAPTER 6

#### TABLE OF CONTENTS

6	Internet Data Management-----	48
6.1	Internet Data Management System (IDMS) Overview-----	48
6.2	IDMS Core Security Dimensions-----	49
6.2.1	Authentication and Authorization-----	49
6.2.2	Non-repudiation-----	51
6.2.3	Data Integrity-----	51
6.2.4	Confidentiality-----	52
6.2.5	Backup / Recovery, and Availability-----	53
6.3	Security Policies Documentation-----	53
6.3.1	Security Polices and Procedures-----	53
6.3.2	Risk Assessment and Mitigation-----	54
6.3.3	Disaster Recovery Plan-----	54
6.3.4	Auditing Policies and Procedures-----	55
6.4	Quality Control and Assurance-----	55
6.4.1	Studies and Reports-----	55
6.4.2	Clinical Coordinators-----	57
6.4.3	Principal Investigators-----	58
6.4.4	Core Laboratories-----	58
6.4.5	Data Coordinating Center-----	58
6.4.5.1	IDMS-----	58
6.4.5.2	Clinical Site Visits-----	61
6.4.6	BBB Investigators-----	63
6.4.6.1	DCC Site Visits-----	63
6.5	Data Collection Forms-----	63
6.5.1	Paper Forms Validation Rules-----	63
6.5.2	Form Revisions-----	64
6.6	Core Laboratory Data Management-----	65
6.6.1	Specimen Tracking-----	65
6.6.2	On-site Monitoring-----	66
6.7	CT Image Data Management-----	66
6.7.1	Data Acquisition, Shipment, and Tracking Data-----	66
6.7.2	Software Considerations-----	67
6.7.3	Hardware Considerations-----	67
6.7.4	Image Acquisition and Initial Clinical Center Storage-----	68
6.7.5	Image transfer to DCC-----	68
6.7.6	Processing of CT Scans-----	69
6.7.6.1	Image Quality Scrutiny-----	69
6.7.6.2	Storing CT Scans-----	70

## **6. Internet Data Management System (IDMS)**

### **6.1. IDMS Overview**

Data coordination is an extremely important facet of the Beryllium BioBank (BBB). With data and specimens transitioning between multiple institutions, it is of paramount importance to have a systematic, coordinated approach to data acquisition conjoined with the highest achievable standards of quality and security. The BBB will have a Data Coordinating Center (DCC), operated at the Colorado School of Public Health, University of Colorado Anschutz Medical Campus (UCD). The DCC is responsible for the logistics of data collection and management, quality control measures and descriptive data analysis. Under the direction of a Steering Committee, the DCC will create a web-accessible database that will allow clinical centers and cores laboratories to enter data into a centralized data collection system. The data collected by the DCC will be maintained on secure servers in Denver, Colorado, with appropriate levels of security and data backup, described below and in the MOO.

The web-accessible database will incorporate a fully functional Internet Data Management System (IDMS) that will be used by the Clinical Center staff, Core Laboratory staff, as well as by the members of the DCC. Essentially, the IDMS is a front end user interface to the DCC backend secure database structure. The IDMS will serve to provide an access portal for BBB data entry as well as ad hoc reporting. Additionally, it will facilitate data entry, quality assurance and data flow management. Clinical Center staff will have responsibility for data entry (and correction, if necessary) of all biobank forms and laboratory data. Limited data sets from the

Core Laboratories (SCL AND GPCL) will be transmitted electronically to the DCC using the BBB IDMS. The DCC has responsibility for editing, in compliance with well-defined regulated standards, and storing of all received biobank data.

The IDMS provides the following basic functions:

1. Data entry and correction of forms with built-in error checking through screens that resemble the forms
2. Display and printing of keyed forms
3. Central edit of keyed forms resulting in locally printed queries
4. Direct entry of information into the central database which is backed up daily at the DCC (once every two weeks back up files are sent off site)
5. Online inventory display of participant materials and their status
6. Ad hoc reporting of biobank related materials

## **6.2.IDMS Core Security Dimensions**

Even though data entered into the DCC IDMS will be de-identified, further data security and integrity standards will be introduced into the biobank website. The core security components of any web-based system such as the DCC IDMS are authentication and authorization, nonrepudiation, data integrity, confidentiality, backup / recovery, and availability. These core items are addressed below.

### **6.2.1. Authentication and Authorization**

Authentication refers to the DCC being able to identify the identity of the parties gaining access to the IDMS; and that only those qualified can gain such access.

Authorization ensures that the authenticated parties are allowed access only to areas of the IDMS that they have been designated access into.



As with any secure website, the first layer of protection is with username and password authentication. Primary Investigators (PI's) can only be granted a username / password by direct request to the DCC. Once a PI has access to the IDMS, only that PI can create Clinical Center and Core Laboratory personnel for the specific site location they represent. In other words, Clinical Center and Core Laboratory personnel can only gain access to the IDMS after a PI has created their respective user account.

Passwords for any registered IDMS user at any given level are stored in one-way encrypted form. Passwords are never stored in plain text, and thus not even the DCC will have the ability to know what any given users password is. Passwords for registered users will be required to be changed every 60 days and must meet the minimum password requirements. Minimum requirements include eight - twelve alphanumeric character length, use of at least one numeric value and one special character value (&,\*,%...) accompanied by a combination of upper and lower case letters.

If at any time a registered user has lost his / her password, that person may reset their password by answering a previous self assigned unique question / answer set (i.e. Q: What is your first car? A: 68GTO). In addition to answering the security question, a "noisy image" test will be provided in order to ensure that the given user is in fact human and not an automated computerized "bot" trying to illegitimately use DCC resources.

### **6.2.2. Nonrepudiation**

This refers to the question of “can a user perform an action within the IDMS and later deny having taken that action?” Authentication and authorization plays a significant role in nonrepudiation. By forcing a user to log in for data entry and other DCC activities, we can create a level of accountability. Most every action taken by a logged in user, is recorded as being taken by that user within the DCC database. This in conjunction with an initial digitally signed user agreement will allow the DCC to provide an audit trail on any authorized and non-authorized uses of the IDMS.

### **6.2.3. Data Integrity**

Data Integrity is the ability to ensure that DCC data being displayed, transmitted or received has not been altered by any unauthorized parties. In addition to the above measures, registered users will access data entry pages through a Public Key SSL (secure socket layer) certificate. Registered, logged-in users will be able to recognize this through the use of the “https” protocol. Every data entry page a logged-in user navigates to will begin with the https:// prefix. In simplistic terms, an SSL certificate is an encryption key that allows for the passing of encrypted data to and from a trusted source; and the decryption of that data from a trusted destination.

Protection measures must also be enforced within the internal DCC system architecture in order that no data can be altered without reason or by unauthorized personnel. Strict and fully documented, physical (hardware) and virtual (software) access, authentication and authorization standards will be put in

place with the DCC facilities. Intrusion Detection software will be an ongoing tool utilized to measure for questionable system access that may compromise data integrity.

Data validation also falls under the category of Data Integrity. It is important that actual data being entered is in fact properly validated data. During entry, all data are checked against standard validation rules. For example, if the preprinted codes for responses are 1 to 5, then only 1, 2, 3, 4, 5, not available or null is permitted. Items are checked for the correct format. If a particular lab value is of the form xx.x then entering "8.23" will cause an error. At the end of each session of data entry (original keying or corrections to previously keyed data), the IDMS will automatically initiate an edit of the new or changed data from that session.

At the completion of data entry, a copy of the data entered into the biobank form will be re-displayed to the data entry staff for final approval. It may also become necessary to scan and upload original de-identified hand completed forms for quality assurance purposes. This would allow data entered into the DCC to be verified against original hand written documents.

#### **6.2.4. Confidentiality**

This concept furthers that of authorization. Confidentiality is the ability to ensure that data is only available to those who are authorized to view that data. With this in mind, only registered logged in users have access to view data stored in the DCC database. Only data relevant to a user is viewable by that user. In other words, data entry staff from any given site location can only view data relevant to his/her site location and system access level.

Concerning a given biobank participant, all data must be de-identified in order to be stored in the DCC biobank. The DCC data entry system has been developed in such a way that entry of any identifying data is not allowed. An exception to this rule is in open text areas, where data entry staff has the ability to enter comments, notes and test descriptions. Large warning messages will be clearly displayed in these sections stating that no identifying data is to be entered. These sections will also be regularly audited for any identifying data; if any are found, the offending data will be purged immediately.

#### **6.2.5. Backup / Recovery, and Availability**

Standard differential backup practices will be utilized for DCC backup policies. A daily, weekly and monthly rotation will be in practice. Offsite storage for archived media will be provided.

In addition, the DCC architecture provides for a “failover” clustered system. In this system, if the primary web / database server fails, a secondary server located in a separate environment will take over for the failed services of the primary server. This will allow for the “high availability” standard required by the DCC biobank website.

### **6.3. Security Policies Documentation**

The following documentation will be maintained by the DCC in order to regulate the IDMS:

#### **6.3.1. Security Policies and Procedures**

It is vital that any system such as the DCC IDMS have a robust security document in place. This document will provide DCC staff and relevant site

participants with direction to maintain the highest level of security throughout the BBB lifetime. This document will outline the following: Network Security, Authentication and Authorization, Data Integrity, System Security / Patch Management, Backup and Recovery and Intrusion Prevention / Detection.

### **6.3.2. Risk Assessment and Mitigation**

HIPAA mandates the relevance and scope of necessary risk assessment and mitigation within any health care organization. In order to properly manage risk factors, these factors must be fully identified in compliance with HIPAA regulations. In accordance, regular risk assessments will be conducted by the DCC concerning the DCC IDMS and its core. These assessments will be fully recorded within the security policies documentation of the DCC. Subsequently, proactive and reactive standards will be updated or added to the security policies documentation in reference to the risk assessment findings. Considering factors during each risk assessment will include, but are not limited to: Environmental Conditions, Network Security, Authentication and Authorization, Data Integrity, System Security / Patch Management, Backup and Recovery and Intrusion Prevention / Detection.

### **6.3.3. Disaster Recovery Plan**

There is an ongoing exposure to risks and threats, such as acts of data vandalism, nature, and war. A Disaster Recovery Plan (DRP) puts in place a “hot site” that can replicate the functionality and services of the DCC IDMS and data structure. The “hot site” will be satisfied through the aforementioned clustered

failover system architecture. The DRP will fully document procedures to maintain and utilize this “hot site” through the DCC.

#### **6.3.4. Auditing Policies and Procedures**

Along with front-end data and user validation, scheduled audits will be conducted to ensure DCC data integrity. The Auditing Policies document will provide the details needed in order to conduct relevant auditing of data, users and sites involved in DCC data entry and specimen contribution on a defined schedule.

### **6.4. Quality Control and Assurance**

Quality Assurance is the responsibility of all BBB involved parties. In order to uphold the standards established for quality assurance regular auditing must be recognized. Each stakeholder of the BBB DCC will be responsible for auditing of pre-defined areas. These areas are listed in the below sections.

#### **6.4.1. Studies and Reports**

Participant recruitment will be closely monitored through up to the minute current data reports accompanied by monthly, quarterly and yearly progress reports. These reports will summarize overall data for a particular site as well as the overall data for the BBB. As a foundation, each report will include recruitment, submission of specimens, submission of CT scans, and submission of data collected at the Clinical Centers, edit status of the data, and quality of submitted materials.

Below are some specifics on the ways performance and quality control statistics will be presented:

**Recruitment:** All Clinical Centers are expected to recruit their target number of patients per month.

**Specimens, CT Scans and Forms:** Performance is assessed by consideration of the following at quarterly intervals.

- For enrolled patients, the number of biobank forms which are past due at the DCC, based on the date of enrollment
- Specimens and CT scans that are past due at the SCL and GPCL or DCC
- Procedures which are required for by Protocol but were not performed
- Reports on data from the SCL and GPCL showing the number of specimens:
  - Received in good condition (frozen, fixed, etc.)
  - Meeting other required QC controls
- Reports on data from the DCC showing:
  - Quality of scans
  - Image counts
  - Other required QC controls

As indicated above, performance reports include summary statistics for each Clinical Center. Large changes in these statistics from quarter to quarter within a Clinical Center may indicate changes in the way data are being collected. Period-to-period changes will be monitored using Shewart plots. Comparison of these statistics across Clinical Centers could suggest either differences in how data are

collected or differences in the participant population, and may prompt further investigation.

**Reliability Studies:** A sample of the de-identified, completed biobank forms from each Clinical Center will be forwarded to the DCC and entered into the central database by DCC staff. Specific forms will be requested on a regular schedule for this quality control program. The Clinical Center data file will be compared to the DCC file, and the number of errors will be tabulated by whether the error was made by CC staff or DCC staff. Systematic errors will be brought to the attention of the staff making these errors. A summary of these comparisons will be included in the Quarterly Performance Report or in a numbered memorandum. If the error rate for keying goes above 0.5% of the total of all keystrokes, DCC staff will notify the CC PI and the SC that there may be problems with the way data are being entered into the central database.

#### **6.4.2. Clinical Coordinators**

In addition to presenting regular ad hoc reports, the IDMS will allow for clinical coordinators to double check their work at several stages. First, when a clinical coordinator has finished entering data on a specific form, that coordinator will be prompted to save any and all changes. If the coordinator chooses to save his / her data, that data will be redisplayed to the coordinator for final approval before submission to the DCC database.

All participant data remains in an editable state until a coordinator finalizes and locks that participant's data set. When a coordinator chooses to finalize a data set a summery check is presented to the coordinator. The summery check will



allow the coordinator to review, in summery form, all critical data relevant to the data set. Only after a coordinator has checked off that the data set has been reviewed can a data set be finalized and locked.

### **6.4.3. Core Laboratories**

Core laboratories will have the responsibility of checking the quality and quantity of blood, lavage, and tissue specimens, and storing samples in the appropriate environment.

### **6.4.4. Data Coordinating Center**

#### **6.4.4.1. IDMS**

Automated auditing on data fields identified as 'key fields'.

The DCC will communicate data queries by alerts that appear on the home page for each site (clinical coordinator and principal investigator). An audit trail is automatically created when the query is issued. When data entry queries have been reconciled by the clinical center and any errors corrected in the database, a response to the data query will be generated back to the DCC in the system, allowing the DCC to confirm the edit, complete the audit, and close tracking of the query. A log of data errors and queries will be maintained and reviewed by the DCC and Steering Committee.

The DCC will be required to audit a 3% sample of finalized and locked participant data sets submitted by clinical coordinators at their assigned site location. This 3% sample will be chosen randomly. Each chosen data set will

be assigned a status of “review” and will retain that status until the given DCC checks off that it has been reviewed.

There are certain activities DCC staff will carry out internally to insure the quality of the data and analyses that are presented to the BBB investigators.

- a. Persons (such as the PI, Project Manager or other DCC staff) not involved in the development of the data editing programs fill out several biobank data forms, making deliberate errors. These forms are keyed and processed through the IDMS data editing system to see if all of the errors are detected by the IDMS.
- b. A sample of original data forms are compared against the data on the DCC computer (as part of repeat data entry). This procedure is used not only to detect data entry errors, but also to detect problems with the editing software developed and implemented by the DCC.
- c. For each continuous variable on the database, a point frequency distribution (i.e., a tabulation of the frequency of occurrence of every distinct value) is obtained. This helps to identify many types of abnormalities in the continuous data such as: (a) digit preferences; (b) bimodality or other distinctive shapes of the distribution; (c) outliers (i.e., extreme values distinctly separate from the rest of the distribution); and (d) incorrect use of missing value codes. Once an observation has been identified as a true outlier, the first step is to go back to the original records and determine whether a recording or keying error was made. If such a value has been verified as correct through the distributed data system, an

inquiry is made as to the reasons an outlier exists. The question of whether or not to include the value in the data analysis depends upon the nature of the analysis. There is no reason to exclude the value if the analysis is a count of the number of participants having a value exceeding a given cut-point. However, if measures of central tendency and variability are being computed, or if correlation or regression analyses are being carried out, non-parametric statistics may be preferable.

- d. When preparing data reports, different tables, which may have resulted from a variety of analysis programs, are checked for consistency of denominators.

Reliability measures are easily interpretable by Clinical Center staff if they are presented as graphical presentations or in tabular form. For example, for continuous variables, the DCC will present scatter diagrams with the correlation presented on the graph, using standard presentation methods.

#### **6.4.4.2. Clinical Site Visits**

Contingent on levels of funding for the biobank, initial site visits to each BBB Clinical Center will be conducted in year one and subsequent visits on an as-needed basis, to be determined by the DCC and Steering Committee. Plans for site visits will be provided to the BBB Steering Committee, DOE Project Officer, DCC Project Officer, and BBB Chair on a schedule agreed to with the DOE Project Office. The site visit teams will consist of a core group of professionals working on BBB, a member of the DCC, and a representative from DOE.

A report summarizing the findings of the site (audit) visit will be sent to the Steering Committee, the Clinical Center Principal Investigator, and the DOE Project Officer.

The components of the site visit will include the following activities:

1. Patient recruitment –

The Clinical Center's methods for identifying and recruiting eligible patients will be reviewed. An item on the site visit agenda will cover the methods Clinical Center staff use while the patient is being screened, recruited, interviewed, and tested to preserve the risk to disclosing the participation of the patient in the BBB.

2. Clinical Center Operations –

The methods of scheduling and record keeping will be reviewed and biobank files examined.

3. Review of Medical Records and Biobank Forms –

Selected biobank forms for a sample of enrolled subjects will be reviewed. The data on the forms for the subjects will be reviewed. The data on the forms for the subjects will be compared against listings of data on the database at the DCC and against records from the Clinical Center. Consent forms will be reviewed.

4. Retraining, Reinforcement, Standardization of Data Collection

Methods –

These steps will be ongoing and individualized to suit the needs identified for each Clinical Center.

## 5. Data Management Activities –

A. Procedures for data entry will be reviewed as well as the procedures for filing records.

B. The edit system will be reviewed; forms will be examined to determine that the appropriate procedures for making corrections on the biobank forms as well as on the edit message pages are being followed.

The site visit report will be prepared within two weeks of the visit and distributed to the site visit team. If possible, the final report will be submitted to the Clinical Center Principal Investigator, the Steering Committee and the DOE Project Officer within three weeks of the visit. The Principal Investigator of the Clinical Center, if appropriate, will be asked to respond within four weeks of receipt of the report with a summary of the steps taken to implement the recommendations made by the site visit team.

### **6.4.5. BBB Investigators**

#### **6.4.5.1. DCC Site Visits**

DCC site visits will be performed in year one and subsequent visits on an as-need basis, to be determined by the DOE, BBB investigators, and or the Steering Committee. The site team will consist of DOE members, and BBB investigators. The format for these visits will be left to the site visitors. DCC staff will be prepared to provide an overview of biobank operations, and demonstrate what changes have been implemented since the last visit.

## **6.5. Data Collection Forms**

The information recorded and collected on standard biobank forms will provide a large part of the data collected through the BBB IDMS. These forms will be comprehensive and cover all data to be collected. The most current version of any given form can be downloaded and printed by registered users from the IDMS.

### **6.5.1 Paper Forms Validation Rules**

Some of the information collected on BBB patients will be collected by patient interviews. The BBB investigators have designed questionnaires that address potential factors affecting beryllium sensitization and disease progression. The interview is designed to limit the subjects time in participation. Some questions have a “yes/no” component preceding a timeframe component. For example, if a participant is asked if they have ever worked with beryllium alloys, they would first answer “yes” or “no”. If the answer is “no”, the interviewer would proceed to the next exposure question. If “yes”, further questions about beryllium alloys will include the duration of exposure.

Due to the large number of questions anticipated, it will be imperative to have questionnaires that are clearly worded and straightforward to complete. As much as possible, answers will be given in predetermined, defined formats such as yes/no, multiple choice or continuous numeric variables of predefined format. “Open-ended” or text answers will be avoided wherever possible. These types of answers are difficult to process, summarize and interpret for a large sample size.

### **6.5.2 Form Revisions**

During the course of the BBB, it may be necessary to revise a given form. This can occur because, despite prior testing, questions on a form may not be easily understood by the participants, the structure of the form does not “flow” well in routine. In combination with annual reviews of all data forms, modifications to the forms will occur on an on-going basis when problems are identified. These will be initiated either by the DCC or by Clinical Centers through one of several mechanisms: email, steering committee conference calls, coordinator conference calls, site visits, posting to biobank website. Problems identified will be recorded, prioritized according to their potential impact on data integrity, and addressed on an on-going basis, in order of importance. Minor edits to the data forms that do not require immediate attention will be batched on a semiannual or annual basis. Each revised form will be clearly marked with a “published date” time stamp upon upload to the biobank website. A clearly marked memo posted on the DCC website will announce the change. Details of form modifications and resolution of problems will additionally be archived in a change log on the DCC website for future reference. Only the latest version of any form will be available for download through the DCC biobank website. When necessary, retraining will be conducted in the use of forms. It will be necessary that biobank coordinators be instructed to only print forms as a participant is recruited into the BBB. Once forms are revised and approved, DCC programming staff will modify the associated data entry screens on the IDMS.

## **6.6. Core Laboratory Data Management**

### **6.6.1. Specimen Tracking**

The performance of the two Core Laboratories (SCL and GPCL) participating in a biobank will be summarized in quarterly performance reports. This report will include the number of specimens received and processed, the number of specimens not prepared or not labeled properly.

The DCC staff will compare the performance of each core lab to its own past performance and to previously agreed upon biobank standards. Quality control charts (Shewart Plots) will be used to examine the means and frequencies of the assays and evaluations performed over time. An investigation will be undertaken to determine whether any shift represents a change in the population being studied or shift in the methods for performing specified assays.

#### **6.6.2. On-site Monitoring**

Each of the core laboratories will be site visited on a schedule designated by the BBB, and the DOE Project Officer. The site visitors will ensure that the specimens submitted to the SCL and GPCL are in secure locations and that there is an appropriate inventory of all materials received by the staff. During the site visit there will be a review of each of the following activities:

- a. Review of Laboratory Organization and Procedures -- The tracking, processing and storage of specimens/CT scans will be covered and evaluation methods (assays/readings) will be reviewed.
- b. Inventory Inspection – The location of specimens in freezers, temperatures of freezers and the back-up procedures for all freezers will be checked.



- c. Internal Quality Control Programs – The procedures and results of each assay performed in the core laboratory will be reviewed and the steps taken to correct any procedures will be discussed. This will include, but not be limited to: quality of processed DNA, viability of frozen samples for mechanistic studies, and adequate aliquoting of specimens for BBB use.
- d. Maintenance of appropriate laboratory facilities.

## **6.7. CT Image Data Management**

### **6.7.1. Data Acquisition, Shipment, and Tracking Data**

At each Clinical Center, coordinators will obtain copies of CT scan images from their respective radiology department's CT scanners in a format that has de-identified participant-specific data, and in a format that will allow for tracking this image data, and that enables transfer of the anonymized CT data to the DCC. This process will be DVD or CD-ROM based, with unique identifiers. Clinical site-specific software considerations will be addressed by the DCC with the assistance of the Clinical Center staff, and will include thorough testing of the transfer of data from each site to the DCC..

### **6.7.2. Software Considerations**

The participating Clinical Centers are equipped with the capabilities to utilize the general-purpose DICOM received software and image management available with the eFilm Workstation software (Merge eFilm Corporation, Milwaukee, WI; Software Version 1.9. The eFilm Workstation software will enable straightforward connectivity with the various CT scanners or a central archive at

the various Clinical Centers and the suite of software will allow for image browsing, anonymization and export. Tools for the de-identification of images, in compliance with HIPAA regulations, will be utilized to enable rapid conversion of patient identifiers imbedded in the DICOM header information of CT data to anonymous biobank-specific codes.

### **6.7.3. Hardware Considerations**

A Microsoft Windows-based computer with sufficient power and storage capacity to run the eFilm Workstation software, the DICOM header modification toolkit necessary for de-identification of CT images and DVD creation software will be required and is presently available at each Clinical Center.

### **6.7.4. Image Acquisition and Initial Clinical Center Storage**

At each Clinical Center, scans obtained by the BBB will be sent to the IAC from the CT scanner where images are acquired or from the local PACS archive, depending on the most practical method available at each Clinical Center. In most cases, CT examinations will be sent to the DCC as electronic images from an electronic archive (i.e. PACS archive) on disk. Similarly, CT studies available on CD or DVD media from other institutions which meet the imaging criteria for the BBB can be imported, anonymized and prepared for transmission to the DCC. DICOM receiver software will enable these images to be stored locally on a temporary basis. In addition to temporary storage on the IAC, each Clinical Center will also be required to store the original image data acquired by the BBB protocols either to a local archive (eg. duplicate disks) for the duration of the BBB. This local archival is utilized to minimize the risk of data loss.

### **6.7.5. Image transfer to DCC**

The image data stored on the Clinical Centers will be placed on CD-ROM or DVD media, appropriately labeled, and mailed to the DCC for further processing, tracking and final storage. The creation of physical media containing de-identified data presents negligible security risk for the Clinical Center and DCC networks and virtually guarantees that patient confidentiality will be assured. In addition, the very large CT datasets would mandate very large bandwidth requirements for the electronic transfer of images and would be at higher risk for errors, corruption and interruption of transfer than physical media. An added benefit of the physical transfer of image data is the inherent decreased risk in data loss during the course of the biobank, since the original DVD media will be retained and stored at the Clinical Centers as well.

The DCC will provide pre-addressed envelopes and packaging materials as well as specific labeling instructions for the Clinical Center employees involved in the data transfer.

### **6.7.6. Processing of CT Scans**

#### **6.7.6.1. Image Quality Scrutiny**

The task of the BBB is to store CT images of adequate quality to be used by future researchers to examine the relationship between CT scan findings and other clinical phenotype and mechanistic data in the biobank of beryllium-related health effects. It is beyond the scope of the biobank to reanalyze or reinterpret the CT scans that have been submitted. Scans will be stored, as will be the interpretations of those scans provided by board-certified

radiologists from the respective clinical institutions. All interpretations by the local radiologist will be placed in the data base. The data form will include expected and unexpected pulmonary findings pertinent to clinical characterization.

A board-certified radiologist and specialist in CT imaging of chronic beryllium disease will serve as an advisor, reviewing selected CT scan images that have been imported into the BBB database

#### **6.7.6.2. Storing CT Scans**

Upon arrival at the DCC, CT data from the media created at the Clinical Centers will be loaded onto a workstation. The Clinical Coordinator will verify the receipt of images at the DCC through the BBB tracking database hosted at the DCC.. The verification of biobank information and image count by the DCC staff will trigger messaging to the Clinical Center coordinators that would allow locally stored images on Clinical Center to be deleted.

In the event that the tracking information hosted in the DCC indicates errors or incomplete information from the Clinical Center was received, the appropriate Clinical Center Coordinator will be contacted to determine if a problem has occurred. For example, errors might include failure to send DVD-ROM materials, errors in DVD creation, incomplete biobank data received by the Center, or perhaps the incorrect biobank was sent to the Center. .

**BERYLLIUM BioBANK (BBB)**

**PROTOCOL  
CHAPTER 7**

**TABLE OF CONTENTS**

	<b>PAGE</b>
7. STUDY ADMINISTRATION-----	72
7.1. Organization Overview-----	72
7.1.1 Department of Energy-----	73
7.1.2 Study Chair-----	73
7.1.3 Clinical Centers-----	73
7.1.4 Data Coordinating Center-----	73
7.1.5 Specimen Core Laboratory-----	73
7.1.6 Genetics and Plasma Core Laboratory-----	74
7.2 Committees-----	74
7.2.1 Steering Committee-----	74
7.2.2 External Protocol Review Committee-----	74
7.2.3 Research Review Committee-----	74
7.3 Web Pages-----	75
7.3.1 Study Specific Web Page-----	75
7.3.2 General Web Page-----	77

## **CHAPTER 7**

### **STUDY ADMINISTRATION**

#### **7.1 ORGANIZATION OVERVIEW**

The BBB will be conducted by the collaborating investigators of five Clinical Centers (CC), a Data Coordinating Center (DCC), two Core Laboratories (a Specimen Core Laboratory (SCL)) and a DNA Core Laboratory (GPCL), with oversight by both the DOE Program Office and the Steering Committee Chair.

The External Protocol Review Committee (EPRC) will be responsible for evaluating the feasibility and comprehensiveness of the BBB Protocol. They will review the Protocol prior to subject recruitment and will review any subsequent modifications to the Protocol. The EPRC will make recommendations to the Steering Committee to edit the BBB Protocol, and consent materials to ensure all biobank policies and procedures are valid and safe.

The Steering Committee (SC) will be composed of the DOE Project Officer, the Steering Committee Chair, the Principal Investigators of the Clinical Centers, the DCC, the SCL and GPCL. This committee will be the focus for discussions and decisions on study design and performance. This committee forms the basis of distribution lists to ensure that all study staff receive the necessary materials to be trained in study procedures and information on the implementation of study procedures.

The DCC will compile an address directory that identifies the name, address, phone and fax numbers, and e-mail address of all Clinical Centers, Core Laboratories, DCC, DOE staff and all committee members. This address directory will be e-mailed to all BBB study investigators and staff, and posted to the BBB Web page. This directory will be updated as needed to reflect staffing changes in the BBB.

Once the study is underway, the DCC support staff will take primary responsibility for presenting information on the progress of the study with respect to collection, analyses, completeness and quality of required data. BBB support staff will be responsible for setting up meetings and conference calls of the BBB including the identification of the meeting site, meeting rooms, distribution of materials, and recording

of minutes. All study materials and minutes not classified as confidential will be uploaded to the BBB Web page.

#### **7.1.1 Department of Energy**

This study is being funded by the U.S. Department of Energy (DOE). The DOE Project Officer is responsible for overseeing the study design, implementation, data quality and information dissemination.

#### **7.1.2 Study Chair**

The DOE has appointed a study chair (Dr. Paul Scanlon) to assist the DOE Project Officer and oversee the operation of the BBB. Dr. Scanlon is not a staff member at any BBB participating institution.

#### **7.1.3 Clinical Centers**

The Principal Investigators of the Clinical Centers have agreed to abide by the Protocol, to have comparable staff, facilities and equipment and to ensure the proper conduct of the BBB including: recruitment and characterization of the patients as specified in the Protocol, accurate data collection and the transmission of information and specimens to the DCC and Core Laboratories.

#### **7.1.4 Data Coordinating Center**

The Data Coordinating Center (DCC) is responsible for data management, study monitoring, quality control measures and descriptive data analysis. The DCC will be responsible for all documents and the BBB Web pages. The DCC will be responsible for providing all Clinical Centers with appropriate identifiers to be used to de-identify patient specimens and data. At the end of study, the DCC will become the long-term storage facility for the data collected as a result of this study.

#### **7.1.5 Specimen Core Laboratory**

The SCL will be responsible for developing the standardized procedures to be used in obtaining the lung tissue from biopsies, peripheral blood for blood cell pellet cryopreservation, BALF, BAL cells for cell pellet cryopreservation and other biological specimens. This includes supplying tissue collection kits and appropriate shipping instructions for the Clinical Centers, receipt of all specimens, except for blood collected for DNA extraction, division and cataloging of specimens, and long-term storage of

specimens. National Jewish Health will house this core facility. The SCL will become the long term storage facility for all specimens at the end of the study.

#### **7.1.6 Genetics and Plasma Core Laboratory**

The DNA core laboratory will be responsible for processing and storage of blood products procured for plasma and the isolation and purification of DNA in the study. This includes supplying tissue collection kits and appropriate shipping instructions for the Clinical Centers, receipt of blood collected for plasma and DNA extraction, division and cataloging of specimens, and short-term storage of specimens. The Hospital of the University of Pennsylvania will house this core facility. The GPCL will provide NJH with the specimens at the end of the study.

### **7.2 COMMITTEES**

#### **7.2.1 Steering Committee**

The Steering Committee (SC) consists of: The DOE Project Officer, the Study Chair, the Principal Investigators of each of the five Clinical Centers, the Principal Investigator of the Data Coordinating Center and the Principal Investigators of the SCL and GPCL (both of whom are also PIs for Clinical Centers). The Steering Committee has the responsibility for developing the Protocol, study implementation, recruitment and Protocol adherence.

#### **7.2.2 External Protocol Review Committee**

The External Protocol Review Committee (EPRC) will be appointed by the DOE Project Office and charged with the duty of reviewing the BBB Protocol prior to recruitment. This committee will offer an independent, unbiased review of the BBB Protocol to ensure scientific soundness and subject safety. At least annually, the EPRC would review proposed modifications to the BBB Protocol.

#### **7.2.3 Research Review Committee**

At the end of the three-year recruitment period, after the BBB has collected a sufficient number of specimens, a Research Review Committee (RRC) will be formed and will be responsible for reviewing proposals, from both BBB and external investigators, for the use of these specimens. The RRC will consist of the Principal



Investigators from each Clinical Center (n=5), a DOE representative, the Steering Committee Chair as well as a majority (n >=6) of scientists and physicians invited by DOE and DCC to sit on the committee. The RRC will meet by teleconference at least quarterly or more frequently if required for the first 3 years following the transfer of the Biobank to DCC to review Research Applications. The proposals will be reviewed and accepted taking into account the scientific merit, feasibility, ability to inform the beryllium community at large, and best use of available/remaining specimens. Approval/rejection of proposals will require vote by simple majority, each Principal Investigator will State/Declare any Conflict of Interest as it relates to the review of the specific proposals and in general to the function of the RRC. If a Principal Investigator participating in the BBB chooses to submit a study proposal, they will recuse themselves from participating in discussions and voting of the said proposal. Upon approving a request based on the RRC recommendation, the DOE will instruct the DCC and NJH to release the appropriate specimens and data for shipment to the investigators for approved research.

### **7.3 WEB PAGES**

The DCC will design and maintain Web sites for the BBB: a study-specific Web site for BBB investigator use only. A second, general Web site will be developed. This site will be accessible by the general public. All Web pages will be located on the Colorado School of Public Health server and will be regularly updated with the most current information available.

#### **7.3.1 Study Specific Web Page**

The study-specific Web pages housed at the DCC will be designed to facilitate the browsing of study documents, printing of current versions of study forms, and entry and update of study data. Users access the study Web page by entering the IP address of the DCC Web server into the address box on their browser. They are then required to log in with a certified username and password.

The Study Home Page identifies the categories of information available on the Web page and provides links to those sections. Most documents will be presented in Adobe Portable Document Format (PDF) to allow users with different PC platforms to

easily access the document, and to limit the level of editing that can be done to the document. The different pages available from the home page are:

**Protocol/Manual**

The Protocol, Procedures Manual and related documents in PDF format

**Memos**

Important study issues distributed as numbered memos

**Minutes**

Minutes from study meetings and conference calls

**Q & A**

Frequently asked questions about the study as well as contact information

**Forms**

Study forms available for printing

**Form QxQs**

Instructions (Form QxQs) for each form provide specific details about each item on the form. These instructions are available in HTML (Hyper Text Mark-up Language) during Internet Data Entry or for browsing on the Form QxQs page.

**Study Tools**

Study schedules, timelines and other study management tools and scripts

**News & Events**

Announcements of upcoming events as well as the study newsletters

**Presentations**

Slide sets for conference presentations, background literature, overview of Protocol, and data management training, etc. Presentations are in PowerPoint. There is a link to the Microsoft download site where the PowerPoint viewer is available for free to users who do not have PowerPoint.

**Reports**

Study reports such as Recruitment Reports and Quarterly Performance Reports

**Publications**

Published publications as well as manuscripts in progress in MS WORD format

**Form Entry**

Users must apply for “Data Entry and Content” and must pass a test on the system to have access to Form Entry on the Web Site. This section heading will be listed on the Home Page only for users who have completed these requirements.

### **7.3.2 General Web Page**

The DCC will design an BBB Web page accessible to the public. This page will be linked to appropriate DOE Web pages. This page will present the goals and methods of the BBB, the BBB investigators and centers, and BBB publications. There will be detailed instructions and forms for non-BBB investigators who wish to request specimens for their own use.

**BERYLLIUM BIOBANK (BBB)**

**PROTOCOL  
CHAPTER 8**

**TABLE OF CONTENTS**

	<b>Page</b>
8. POLICY MATTERS -----	79
8.1 Training and Certification-----	79
8.1.1 BBB Training Sessions -----	79
8.1.2 Consent Administration-----	79
8.1.3 Internal Data-----	79
8.1.4 CT Technician and Scanners -----	80
8.1.5 Tissue and specimen collection technicians -----	80
8.1.6 Questionnaire Administration-----	80
8.1.7 Other Functions-----	80
8.2 Release of BBB Data or Specimens -----	80
8.3 Conflict of Interest Policy-----	82
8.3.1 General Principles -----	82
8.3.2 Individuals to be Governed by These Guidelines -----	82

## **CHAPTER 8**

### **POLICY MATTERS**

#### **8.1 TRAINING**

##### **8.1.1 BBB Training Sessions**

Prior to patient recruitment, all BBB Clinical Center staff are expected to attend a central training session. This may be conducted in person or by teleconference/web, depending on study funding considerations. At that time, the BBB Manual of Operations (MOO) will be reviewed in detail. All training session materials will be posted on the BBB Web page for future reference. Clinical Center staff joining the BBB after this training session should review these materials and receive training from previously certified clinical staff. As needed, additional training will be provided by designated core personnel at Steering Committee meetings and site visits. The training sessions will focus on both procedural/logistic issues, including consenting, questionnaire administration, specimen handling, data abstraction, data collection, data entry and quality assurance.

##### **8.1.2 Consent Administration**

All BBB staff that will be consenting subjects will require documentation of training in the ethical conduct of research. Additional training will be provided by designated core personnel regarding the consent form, and the process of consent in an attempt to ensure uniformity of consent across all Clinical Centers.

##### **8.1.3 Internet Data Entry**

All Clinical Center staff performing data entry will be required to undergo certification before being allowed to key or correct data in the IDMS. This will include the accurate keying and correct updating of sample forms into the IDMS.

**8.1.4 CT Technicians and Scanners**

Prior to any BBB CT scan acquisition, the DCC will conduct a practice data transfer session at each Clinical Center. This may be done on site or by teleconference, depending upon funding considerations. Test CT's will be transferred to portable storage medium and forwarded to the DCC for assessment of retrieval and compatibility

**8.1.5 Tissue and specimen collection technicians**

Prior to collecting any BBB biopsy specimens, a Clinical Center coordinator will participate in training session designed to ensure all study personnel receive standardized instruction on the retrieval of specimens and procedures to handle, label and to ship the specimens to the SCL and GPCL.

**8.1.6 Questionnaire Administration:**

Questionnaire data will be obtained from interviewer administered questionnaires covering medical information, and work and exposure history. To insure that uniform information and data is obtained from all subjects, BBB staff will provide training to those administering the questionnaires in this process. This will include training from an Industrial Hygienist in the administration of the exposure questionnaire.

**8.1.7 Other Functions**

All venipuncture will be performed by hospital staff certified by the Clinical Center to perform these activities.

**8.2 RELEASE OF BBB DATA OR SPECIMENS**

The RRC reviews each request and the following principles are addressed in determining the disposition of each request .

1. Overlap with previously approved data bank studies.

2. The scientific importance of the request.
3. The efforts and costs of providing the information.
4. The willingness of the individuals submitting the request to accept the limitations, as specified by the DOEDCC, on the uses that can be made of the data and data analysis.
5. The appropriateness of the request as it relates to the number and types of specimens that have been acquired to date.

This RRC will be responsible for reviewing requests from study BBB Investigators as well as non-BBB Investigators and making a recommendation DCC for specimen and data use. The decision for release of the data and specimens will be based on the availability of specimens, the scientific goals of the proposal and the order the requests are received after public notice has been issued to announce the availability of the specimens.. This policy will remain in effect as long as there are specimens to release.

## **8.3 CONFLICT OF INTEREST POLICY**

### **8.3.1 General Principles**

The BBB investigators have agreed to a policy on conflict of interest that has few specific restrictions, but a broad indication for disclosure of potential conflicts of interest. The BBB investigators wish to endorse the spirit and content of the 21st Bethesda Conference: Ethics in Cardiovascular Medicine (Frommer et al, 1990) dealing with these issues, and seek to make this policy consistent with the record of that conference.

To address actual or perceived conflict of interest in the BBB, the participating investigators voluntarily agree to abide by the guidelines described in the policy

statement developed for the BBB. Specifically, BBB principal investigators or their colleagues shall exercise no preferential access to store specimens or stored data. Their requests will be subject to review by the RRC, as for non-BBB investigators. See the Manual of Operations for a copy of the Conflict of Interest Statement and additional details on these matters.

### **8.3.2 Individuals to be Governed by These Guidelines**

Members of the BBB Study Group who will be governed by these guidelines include the Study Chairman, the Principal Investigator at each Clinical Center, key personnel in the Data Coordinating Center, and the Principal Investigators of the Core Laboratories. Co-Investigators and other staff who have major responsibility for enrollment, recruitment, follow-up or collection of data for the BBB at Clinical Centers or Core Laboratories will also be governed by these guidelines. The Principal Investigator for each BBB Center will submit a list of individuals who will be governed by these guidelines at the beginning of the study and revise, as necessary, annually. The Principal Investigator of each participating unit will review the guidelines with all appropriate staff prior to the start of patient recruitment and at least annually thereafter.



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