

Version 4.0



**LONGITUDINAL STUDIES OF HIV-ASSOCIATED
LUNG INFECTIONS AND COMPLICATIONS
(LUNG HIV)**

MANUAL OF OPERATIONS

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CHAPTER 1**OVERVIEW OF LONGITUDINAL STUDIES OF HIV-ASSOCIATED
LUNG INFECTIONS AND COMPLICATIONS
(LUNG HIV)****A. PURPOSE**

The National Heart, Lung, and Blood Institute (NHLBI) established the Lung HIV project as a collaborative multi-site study to examine a broad range of separate yet overlapping pulmonary topics (Appendix A.) Eight Clinical Centers and a Data Coordinating Center (DCC) have been tasked with creating a collection of datasets and biological specimens for use during this RFA and in future investigations. The program is structured to facilitate both the development of these shared resources and the completion of the individual projects. Results of these efforts will be disseminated through publication in leading medical journals.

The concept of the Lung HIV study was developed by NHLBI to efficiently support multiple R01 efforts while simultaneously creating a shared database and specimen repository. The Lung HIV program will build on the knowledge and experience from existing studies and facilitate the start-up of new studies to further the understanding of the relationship between pulmonary disease and HIV infection.

The Lung HIV mission is to achieve a clear understanding of the clinical manifestations of HIV-associated pulmonary complications by fostering multidisciplinary research collaboration and establishing a high quality centralized specimen repository with an associated clinical dataset based on shared definitions.

The Manual of Operations (MOO) documents the procedures to be used to conduct the core elements of the Lung HIV Study. As these procedures are modified, the DCC will prepare and distribute (via postings to the Web page) revised chapters as necessary. Additionally, a numbered memo will alert Lung HIV staff to the change. Every participating institution is expected to have several copies of the MOO available for ready reference.

During the course of using this manual, Lung HIV staff members are encouraged to send feedback to the DCC that will improve the MOO. Every effort will be made to provide procedure instructions that are clear and complete. This will provide the highest quality data for future analysis. When a chapter is revised, a new chapter should be printed from the Web page, inserted into the manual and the old chapter destroyed. A three-ring binder is recommended for storing the MOO.

B. PARTICIPATING INSTITUTIONS

The Longitudinal Studies of HIV-Associated Lung Infections and Complications (Lung HIV) Study is being conducted by the National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH), in collaboration with eight Clinical Centers, a Data Coordinating Center (DCC) and a Specimen Repository. Each of the Clinical Centers, the Data Coordinating Center, and the Specimen Repository have been contracted by NICHD to perform certain duties for the study.

Detailed contract information on all study staff at all the participating institutions is provided in the Lung HIV address directory. This directory is updated as needed, distributed by e-mail and posted on the Lung HIV Web site.

1. NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI)

As the contracting institution, staff members at the NHLBI in Bethesda, Maryland, are responsible for the overall design and conduct of the Lung HIV Study. The Project Officer will oversee the study design, implementation, data quality and information dissemination. The Contract Officer will monitor the receipt of all deliverables required by the contracts and payments to the contracted institutions.

Contact: Hannah Peavy, MD, Project Officer

2. CLINICAL CENTERS

Each of the eight Clinical Centers has participated in the design of the Lung HIV Study and has agreed to have the necessary staff and resources available for project activities. Each Clinical Center will be responsible for recruiting and retaining subjects, collecting the required data, transmitting these data electronically to the DCC, and shipping specimens to the Specimen Repository.

Contacts:

Richard Chaisson, MD, Principal Investigator, Johns Hopkins University - Medical

Gregory Kirk, MD, MPH, PhD, Principal Investigator, Johns Hopkins University –

Bloomberg School of Public Health

William Rom, MD, MPH, Principal Investigator, New York University School of Medicine

Philip Diaz, MD, Principal Investigator, Ohio State University

Laurence Huang, MD – University of California – San Francisco

Sonia Flores, PhD – University of Colorado, Denver-Anschutz Medical Campus

Alison Morris, MD, MS – University of Pittsburgh

Kristina Crothers, MD –University of Washington

3. DATA COORDINATING CENTER (DCC)

The Data Coordinating Center (DCC) is located at Clinical Trials & Surveys Corp. (C-TASC) in Owings Mills, Maryland and is responsible for study coordination, data management, study monitoring, quality control measures and data analysis. The DCC will maintain all study documents (including forms), the study Web pages and the Internet data entry system (Study CTMS). Additionally, the DCC will schedule conference calls and meetings and distribute the documents necessary for conduct of the same.

Contact: Bruce Thompson, PhD, Principal Investigator – C-TASC

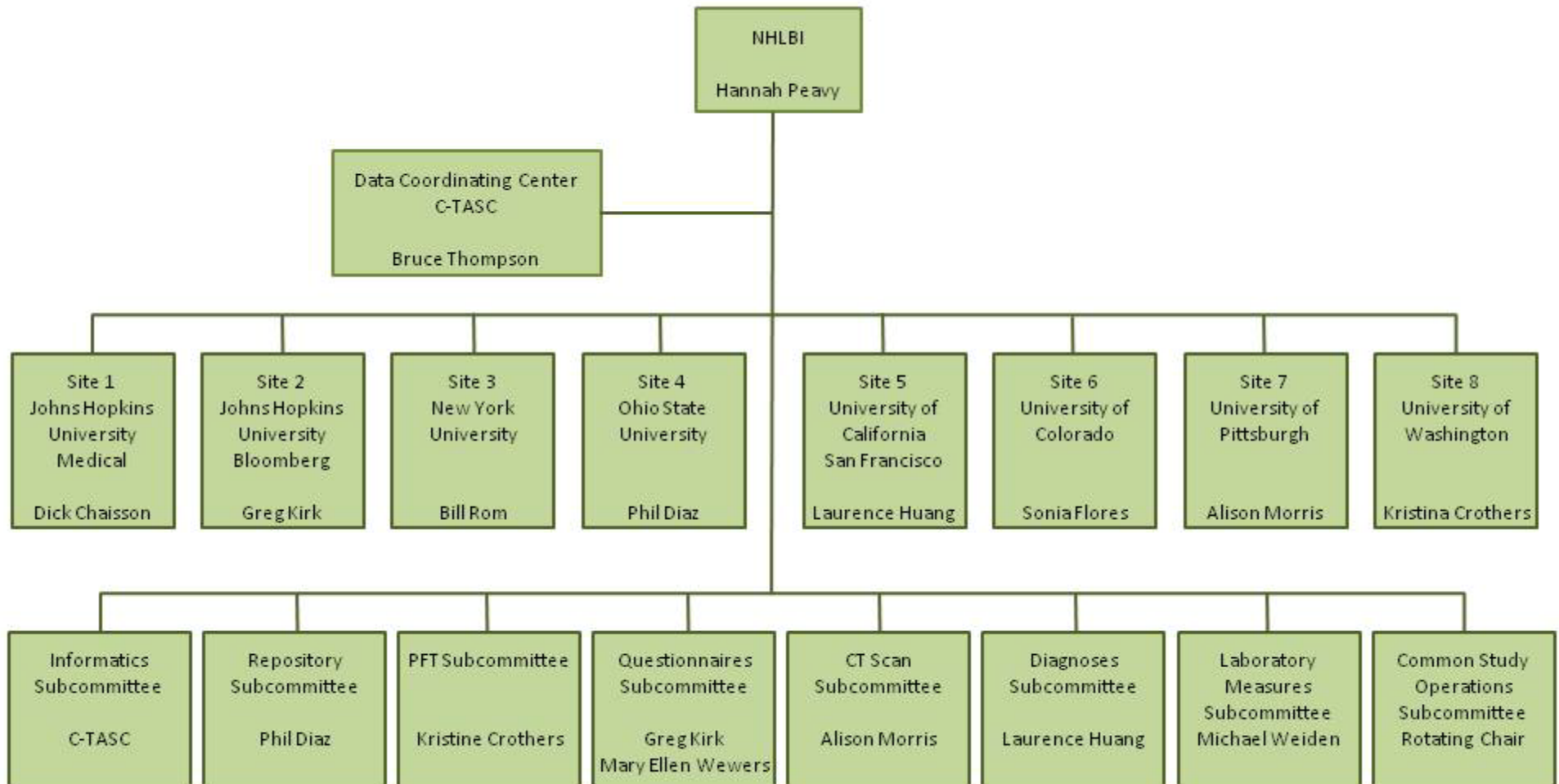
4. SPECIMEN REPOSITORY

The Specimen Repository is BBI SeraCare. The Repository is responsible for receiving, inventorying, and shipping specimens to investigators as well as providing data to the DCC for inclusion in StudyCTMS.

Contact: Elizabeth Wagner, MPH - NHLBI

C. Organizational Chart

Lung HIV Organizational Structure



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CHAPTER 2

ELIGIBILITY CRITERIA

A. SCREENING

Participant eligibility for the Lung HIV Study is confirmed by each site according to the parameters of the individual protocols. The Lung HIV Participant ID number is assigned after informed consent is obtained and data for that subject is entered into the data system.

B. PRIOR REVIEW OF PATIENT RECORDS

Record review and participant recruitment efforts are unique to each site and will be conducted according to the individual protocols.

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CHAPTER 3

INFORMED CONSENT

A. BACKGROUND

Obtaining informed consent is essential prior to involvement of human subjects in research. The purpose of the informed consent process is to protect an individual's rights. The principles guiding this process are those of respect for persons, beneficence and justice. Each center will document the consent process by use of consent forms that have been approved by their institution according to the individual protocol.

B. INSTITUTIONAL REVIEW BOARD (IRB) PROCESS

A prototype informed consent form for Lung HIV study has been developed (Appendix E). Clinical Centers are expected to use or incorporate key elements of this document for submission to their institutional review boards (IRBs) for approval to participate in the Lung HIV Study. Each Study Coordinator must send the final copies of the consent form to be used in their Clinical Center, with their IRB's seal or approval notice, to the DCC prior to initiating patient activities in the Lung HIV Study. DCC staff will compare the local consents to the prototype consents. Specific local additions to and editing of the prototypes may be required in individual institutions, but deletion of material and major rewording of text may need to be explained and justified. Once the consent form has been approved by the local IRB it cannot be changed without resubmitting it for approval. The DCC must likewise be sent a copy of the revised form.

C. CONSENT ADMINISTRATION

The first step of the process is the assessment on the part of the Study Coordinator and/or Principal Investigator of whether the individuals providing consent have the capacity to make this decision. If decisional capacity is impaired, then consent cannot be obtained.

The subject is told about the study procedures, what is expected in terms of time commitment, and the risks and benefits of participating in the study. The consent form contains the required information that is to be disclosed. Each portion of the consent form should be explained in detail. When obtaining consent, the Investigator and/or coordinator should explain the following:

- Purpose of the Lung HIV study
- Purpose of the individual study being conducted at that center
- Procedures: A clear description of the study in terms of the types of measurements that will be taken, the time it will take to make the measurements and the overall length of commitment
- Benefits associated with participation
- Risks, discomforts and precautions. This would include radiation exposures and possible effects of the exercise testing
- Alternatives to participation
- Confidentiality of information
- Availability of information: Subjects should be told who to contact if they have questions about study procedures (the PI) or questions about their rights as a research subject (the chair of the local IRB)
- The right to withdraw from the study at any time

After providing information regarding the procedures, risks and benefits, it is important to give the subject an opportunity to ask questions. Sufficient time must be provided to answer all patient questions prior to signing the consent. It is important to ascertain whether the subject understands and appreciates what they are agreeing to do. Not only does this protect their rights, but it also minimizes the risk of the subject dropping out of the study.

Care should be used throughout the recruitment and informed consent process so a subject does not feel coerced into participation. Subjects should be reassured that their future care at the institution will not be affected should they decide not to participate.

The subject must sign the consent form in the presence of Lung HIV study staff indicating consent to participate in the study. At least one Lung HIV study coordinator or investigator will witness the signature. Additional witnesses may be required by the local IRB. All signatures on the consent form must be in a non-erasable ink. The patient's Lung HIV Participant ID number should NOT appear on the consent. A copy of the signed consent is given to the subject to keep.

D. TIME CONSTRAINTS FOR OBTAINING CONSENT

While a patient may be screened for the Lung HIV Study, no other Lung HIV study interview or procedure may be performed until written consent has been obtained. Consent should be obtained far enough in advance of the surgical procedure to allow for the completion of the Lung HIV study interviews and procedures without interfering with pre-operative preparations or unduly stressing the patient physically or mentally.

E. LUNG HIV STUDY CONSENT HANDLING

The main study consent statement is an "all or none" form. The patient either accepts it in its entirety and signs it, or does not. Neither partial exclusions, nor special exemptions, are allowed in this process. Consenting to the main Lung HIV study may not commit the patient to consent to a Lung HIV procedure under an individual protocol, depending on the Clinical Center.

Signed consent forms are important legal documents. These original forms should be kept in the patient's Lung HIV study file together with his/her other Lung HIV study forms and documents. These forms are not part of the individual's institutional medical records, but part of

his/her participation in the Lung HIV study. Consent forms will be examined during site visits by DCC staff.

F. HIPAA

Each Clinical Center is responsible for administering their institution's HIPAA release form. The original form should be kept in the Lung HIV study file, and the subject should be given a copy.

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CHAPTER 4

PATIENT ASSESSMENT PROCEDURES

A. INTERVIEWS

Advance work by the Clinical Center staff facilitates completion of interviews and reduces waiting time. To be properly prepared for the patient's visit, it is suggested that the Clinical Center staff follow the procedures described below.

The Research Coordinator in each Clinical Center assembles packets so that forms and other materials are readily available. These packets should include a consent form for the potential subject to sign and the appropriate Lung HIV study forms for that visit. The Participant ID number assigned to the potential subject should be written on the forms in the header spaces provided.

At the beginning of the interview, the interviewer determines the potential subject's willingness to participate in the study and, if willing, obtains informed consent. This is estimated to take about one-half hour to complete.

The interviewer then proceeds to the demographic and history questionnaires. This is estimated to take about two hours to complete. All interviews will be conducted in a private, quiet office environment that will facilitate the subject's cooperation and help put the patient at ease.

During an interview, if the subject expresses doubt as to the meaning of a question, repeat it exactly. Emphasizing individual words or phrases often makes the meaning clear. Further explanation may be needed, but do not cross-examine the respondent. When after brief explanation doubt remains as to whether the answer should be "yes" or "no," the answer should be recorded as "no."

B. PULMONARY FUNCTION TESTING

Pulmonary function equipment, procedures, and personnel qualifications are based on the recommendations of the American Thoracic Society (ATS). Spirometry, lung volumes, and diffusion capacity maneuvers at all clinics must meet or exceed ATS standards. Predicted normal reference values will use those derived from NHANES III and will be adjusted for age, sex, race and height. All technicians should be certified pulmonary function technologists (National Board of Respiratory Care) or meet recommendations for personnel qualifications issued by the American Thoracic Society.

C. SPIROMETRY

1. Procedures for Forced Vital Capacity (FVC)

a. Prepare equipment

The equipment is turned on and adequate time for warm-up has been allowed. Any required calibration tests have been performed and are within allowed measurement error.

b. Prepare the patient

- i. Measure and record weight and height without shoes.
- ii. Patient must be seated when tested.
- iii. Nose clip must be worn.
- iv. Patient should loosen any restrictive clothing.

c. Instruct and demonstrate the test to the subject

Emphasize need for a deep, full inspiration, a hard and forceful “blast,” and a complete expiration for at least 6 seconds.

d. Perform maneuver (closed circuit or open circuit method, depending on when mouthpiece is placed in mouth)

- i. Attach nose clip.

- ii. Place mouthpiece in mouth and close lips around the mouthpiece (if closed circuit method).
- iii. Inhale completely and rapidly with a pause of <1 sec at TLC.
- iv. Place mouthpiece in mouth and close lips around the mouthpiece (if open circuit method).
- v. Exhale maximally until no more air can be expelled while maintaining an upright posture.
- vi. Repeat instructions as necessary, coaching vigorously.
- vii. Check test repeatability and perform more maneuvers as necessary.
- viii. Repeat for a minimum of 3 maneuvers. In general, if 3 acceptable and 2 reproducible tests cannot be obtained within 8 attempts, further testing will not be productive, and may be terminated at the judgment of the technician. Inability to perform spirometry should be reported to the investigators because it may affect participation in the study.

2. Procedures for Bronchodilator Testing

- a. Pre-bronchodilator testing: At least 4 hours since last use of short-acting bronchodilator, and at least 12 hours since last use of long-acting beta-agonist, and 24 hours after tiotropium.
- b. Post-bronchodilator testing: Repeat FVC in 10-15 minutes for 3 acceptable tests, and no longer than 30 minutes after inhalation of 4 puffs of albuterol delivered by MDI with spacer (ventilator tubing acceptable).
- c. Administration of bronchodilator:
 - i. Use albuterol (100 µg x 4 doses) via metered dose inhaler with spacer (tube).
 - ii. Activate inhaler in air to check for adequate operation.

- iii. Instruct patient to blow out to RV, then insert the tube into patient's mouth.
- iv. Instruct patient to inhale slowly; technician activates inhaler during the inspiration.
- v. Have patient hold breath for 10 seconds.
- vi. Wait 30-60 seconds, then repeat three more times, for a total of 4 inhalations.
- v. Start timer and test patient 10-15 minutes later.
- vi. If a lower dose is used because of concern for side effects (i.e. heart rate, tremor), this should be recorded on data collection form.

3. Evaluation and Reporting of FVC

a. Acceptability: Within maneuver evaluation

Three acceptable tests are required for an adequate FVC maneuver. Acceptability criteria are listed below, along with suggested criteria for implementing computerized checks.

- i. Slow start of test. Patient did not begin his/her initial peak flow early enough; repeat, coaching for a more forceful and abrupt start ("BLAST it out"). This error occurs when volume at the back-extrapolated zero-time is more than 5% of the FVC or greater than 150 ml, whichever is greater.
- ii. Cough. This causes abrupt irregularities in flow, and is a reason to reject the test when it occurs during the first second of the effort. Coach the patient to make the effort without coughing. Sometimes it is helpful to have the patient blow just slightly less forcefully than the maximum to prevent a cough.

- iii. Abrupt end of test. At the end of exhalation, the patient stopped blowing out too abruptly, ending his/her effort too soon. Coach the patient to maintain his/her expiratory effort to the very end.
- iv. Short expiratory time. Patient did not continue his/her expiration for at least 6 seconds or did not reach a volume plateau. In patients with severe COPD, the expiration often does not reach a plateau in reasonable time. In this case, 6 seconds of effort is the minimal duration of effort but 10 to 12 seconds of effort is reasonable.
- v. Low peak flow. The patient did not achieve an adequately forceful blast. Repeat the effort, coaching to blow harder and faster if possible.

b. Reproducibility: Between maneuver evaluation

Reproducibility criteria are used to determine when more than 3 acceptable FVC maneuvers are needed. Two reproducibility criteria are used to determine how well each acceptable effort compares with the largest acceptable effort. An unacceptable test should be discarded before applying the reproducibility criteria.

- i. FVC variation. The second largest FVC should be within 0.150 L of the largest acceptable FVC.
- ii. FEV₁ variation. The second largest FEV₁ should be within 0.150 L of the largest acceptable FEV₁.
- iii. For those with an FVC of ≤ 1.0 L, both the FEV₁ and the FVC should be within 0.100 L of the largest acceptable values.

c. Choosing data to report:

- i. The largest acceptable FVC and the largest acceptable FEV₁ will be reported. The reported FVC and FEV₁ do not have to be taken from the same maneuver.
- ii. The FEF 25-75% is reported from the acceptable curve with the largest sum of the FEV₁ and FVC.
- iii. Clinics should follow their usual practice if the test session did not yield efforts that met the Lung HIV requirements. If the session, while not in conformance with the Lung HIV requirements, resulted in values which in the lab's usual practice would be considered reportable, the lab should report the obtained values but note on the report that the values did not meet Lung HIV requirements but are considered reportable (the note should specify which requirements were not met). If the session resulted in values which the lab would usually not consider reportable, then the values which did not meet Lung HIV requirements will be missing.

4. Quality Control Procedures for Spirometry:

- a. Daily 3L calibration check for volume spirometers. Value must be within calibration limits ($\pm 3\%$).
- b. Daily leak check for volume spirometers. Volume loss must be <30 mL after 1 minute.
- c. Daily 3L calibration or calibration checks at 3 flow rates for nemotachometer systems. Volume at each flow must meet accuracy requirement of $\pm 3.5\%$.
- d. Quarterly full-scale linearity checks for volume spirometers. Measured volume must be within $\pm 3.5\%$ of reading or 65 mL, whichever is greater.

- e. Normal subjects repeated measures monthly.
- f. Maintain documentation of repairs, computer software or hardware update or changes. If equipment is altered or relocated, document calibration checks and quality-control procedures on equipment before further subject testing.
- g. Monthly leak check for calibration syringes. Calibration syringe has an accuracy of ± 15 mL or $\pm 0.5\%$ of the full scale.
- h. Calibration syringes will be recertified annually for an accuracy of ± 15 mL or $\pm 0.5\%$ of the full scale.
- i. All calibration procedures should be recorded in a manner to allow review.

D. DIFFUSING CAPACITY

1. Equipment

D_LCO will be measured by the single-breath technique using a ten-second breath-hold.

Equipment specifications are summarized in Table 1:

Table 4.1. Equipment Specifications	
Volume accuracy	+/- 3% over 8 L range using test gases, with a test syringe accuracy of 0.5%
Gas analyzers	Linear from 0 to full span within 0.5% of full span. Stable over duration of test with drift <0.5% of a measured gas
Circuit resistance	<1.5 cmH ₂ O/L/sec at a flow of 6 L/s
Demand valve sensitivity	<10 cmH ₂ O for 6 L/s flow through valve and circuit (if compressed gas source used)
Timer	+/- 1% over 10 seconds (100 ms)
Apparatus/valve filter dead space	<0.350 L

2. Procedures for DLCO

- a. Prepare equipment: The equipment is turned on and adequate time for warm-up has been allowed. Any required calibration tests have been performed and are within allowed measurement error.

- b. Prepare the subject, instruct and demonstrate the test
 - i. The subject should be seated comfortably.
 - ii. If clinically acceptable, the subjects should not breathe supplemental oxygen for 10 minutes prior to a standard test.
 - iii. The subject should also be clinically stable, > 30 minutes after exercise, > 2 hours after meal, > 4 hours after alcohol, and without smoking on the day of the test.
 - iv. The time of last smoking should be recorded.
- c. Perform maneuver
 - i. Once the mouthpiece and nose clips are in place, tidal breathing should be carried out for a sufficient time to assure the subject is comfortable with the mouthpiece. Avoid deep inspirations.
 - ii. Have subject perform unforced exhalation to residual volume.
 - iii. At RV, connect the subject's mouthpiece to the source of test gas, and have subject inhale rapidly to TLC.
 - iv. Following a relaxed breath hold, the subject exhales and sample gas volume is collected for analysis following the requirements listed in Table 2 below.
- d. Repeat testing
 - i. At least 4 minutes should elapse between tests to allow an adequate elimination of test gas from the lungs.
 - ii. In subjects with severe obstructive lung disease, a longer interval (10 minutes) between repeat testing should be allowed. If continuous monitoring of expired gas concentration is available, confirm washout of tracer gas from the previous test before the start of the next test.

3. Evaluation and Reporting of DLCO

- a. Standard requirements across centers related to performance are shown in Table 2:

Table 4.2. Performance Technique	
Inspiratory time	90% complete at < 4 seconds
Inspiratory volume	> 85% of maximum of SVC or FVC; check the BTPS/STPD conversion if you are having difficulty achieving this
Breath-hold duration	9-11 seconds
Breath-hold conditions	Relaxed (neither Valsalva nor Mueller)
Washout volume	0.5 L if VC < 2.0 L, otherwise 0.75-1.0 L (BTPS)
Sample volume	0.5 L if VC < 2.0 L, otherwise 0.75 L in < 4 seconds
Inspired FiO ₂	Ambient (0.21), beginning at least 5 minutes before testing
Repetitions	Minimum 2 trials agreeing within 10% or 3.0 mlCO-STPD/min/mmHg of mean, maximum 4/session, > 4 minutes between trials

- b. Choosing data to report
- i. D_LCO (uncorrected for hemoglobin): Mean of at least 2 acceptable and reproducible (within 10% or 3.0 mlCO-STPD/min/mmHg of mean) trials.
 - ii. Altitude-corrected D_LCO (not currently applicable for any Lung HIV site).
 - iii. Inspired volume (V_I; L-BTPS): Mean of 2 efforts which are greater than 90% of VC.
 - iv. Alveolar volume (V_A; L-BTPS): Mean of 2 efforts.
 - v. Values are recorded on the Pulmonary Function Report and the Pulmonary Function Worksheet. Print-outs of values and tracings should be attached to the Pulmonary Function Report Form. Manufacturer and model of the equipment used for each test will

not be recorded on the data collection form, but should be available in the laboratory's file for each patient-test.

- vi. Clinics should follow their usual practice if the test session did not yield efforts that met the Lung HIV requirements. If the session, while not in conformance with the Lung HIV requirements, resulted in values which in the lab's usual practice would be considered reportable, the lab should report the obtained values but note on the report that the values did not meet Lung HIV requirements but are considered reportable (the note should specify which requirements were not met). If the session resulted in values which the lab would not usually consider reportable, then the values which did not meet Lung HIV requirements will be missing.
- vii. Hemoglobin (if measuring) (Corrected D_LCO values will be calculated centrally).
- viii. COHb (if measuring) (Corrected D_LCO values will be calculated centrally).

4. Quality Control Procedures for Single-Breath DLCO

- a. Volume calibration (3 L syringe) and leak testing, if applicable, will be performed daily.
- b. Gas analyzer zeroing will be done before and after each test.
- c. Gas analyzer linearity will be checked quarterly.
- d. Timer accuracy, if applicable, will be checked quarterly.
- e. Standard healthy controls will be tested monthly and their D_LCO on repeated testing should be within 10% of the mean of their previous values.

- f. All quality control data should be recorded in a logbook that should be available for review by site visitors.

E. PLETHYSMOGRAPHY

1. Procedures for Lung Volumes by Plethysmography (TLC, SVC, and FRC(plethys))

Plethysmograph transducer	Accurately measures mouth pressure of $\geq \pm 5$ kPa ($\geq \pm 50$ cm H ₂ O)
Flat frequency response	> 8 Hz
Chamber pressure transducer	Accurately measures a range of ± 0.02 kPa (± 0.2 cm)
Time constant for controlled leak	10 seconds is ideal

- a. Prepare equipment: The equipment is turned on and adequate time for warm-up has been allowed. Any required calibration tests have been performed and are within allowed measurement error.
- b. Prepare and instruct the subject:
 - i. The patient is seated comfortably without extending or flexing the neck to reach the mouthpiece.
 - ii. You may try a short demonstration with the box open by using your hand to occlude the end of the breathing tube. This will allow the patient to experience the feel of the shutter closure before closing the box, while he/she is free to ask questions. You may also get a feel for how well the patient is about to perform.
 - iii. The computer may prompt you to zero the pneumotach. Be sure that the patient is not blowing air near the mouthpiece.

- c. Perform maneuver:
- i. Close the box and wait about 1.5 to 2 minutes for temperature equilibration. You might try a few practice maneuvers during the equilibration period. Then proceed.
 - ii. Properly place nose clip and mouthpiece. Have patient support his/her cheeks with both hands.
 - iii. Quiet breathing for approximately 3-10 tidal breaths to establish a stable end expiratory lung volume (functional residual capacity, FRC).
 - iv. When the patient is at FRC, close the shutter at the end of expiration and have the patient slowly make inspiratory and expiratory efforts against the closed shutter. Try to keep the rate between 20 and 60/min (between 0.5-1.0 Hz). Rapid panting may cause you to overestimate lung volumes in obstructed patients, and frequencies of <0.5 Hz can cause problems with the controlled leak of the body plethysmograph system. The line on the monitor should retrace itself or loop only slightly.
 - v. Repeat for a series of 3-5 technically satisfactory panting maneuvers after which the shutter opens, and the patient performs an ERV maneuver followed by a slow IVC maneuver. If the patient cannot do this, an IC maneuver may be followed by a slow EVC maneuver. If needed, the patient can come off the mouthpiece and rest between TGV/VC maneuver.
- d. Evaluation of plethysmography: Between efforts, look at the closed-shutter lines. Coach the patient if the lines do not look acceptable:

- i. Line too short (the line should extend at least halfway across the graphic display): Coach the patient to suck and blow against the shutter with more force.
 - ii. Lines extend out of the graphic display: Coach the patient to suck and blow with less force.
 - iii. Wide loops: Check for adequate cheek support or ask if the patient closed his/her glottis during the suck/blow. Check to be sure that the plethysmograph door is sealed. In some patients, wide loops may be the best you can get. Fit your line to the inspiratory sides or connect the endpoints of the loops.
 - iv. Nearly vertical line: (no box pressure change, but large mouth pressure change): Patient may be “making efforts” by using only his/her cheeks or tongue with his/her glottis closed. Or the box may be open; check the door.
 - v. Nearly horizontal line: (large box pressure changes, but no mouth pressure change): Glottis is closed or the mouth pressure transducer tubing is disconnected or crimped.
 - vi. Frequency > 60/min: Have patient pant slower. Use a metronome if needed to assist patients with frequency of panting.
- d. Acceptability and reproducibility:
- i. Lung volume (TLC) reproducibility should be within 10%. Continue until you have 3 acceptable and reproducible (within 10% of the largest of the 3) TLCs. If you have done 4 to 6 efforts and are not successful, call in someone else to try. After 8 to 10 total, give up.
 - ii. The SVC should be obtained as a slow expiratory VC maneuver following the TLC measurement. SVC should be repeated until 3

acceptable and reproducible efforts (within 0.2 L) are obtained.

The duration of effort should not ordinarily exceed 12-15 seconds.

- iii. At least three FRCpleth values should agree within 5%. If there is larger deviation, additional values should be obtained until three values agree within 5% of their mean.

e. Choosing data to report (TLC, SVC, and FRC(plethys))

- i. Before picking data to report, you should check the slopes of the lines. THE COMPUTER'S SLOPE (IF AUTOMATED) SHOULD NOT BE ACCEPTED WITHOUT CAREFUL SCRUTINY. COMPUTER ALGORITHMS FOR PICKING SLOPES ARE STILL NOT AS GOOD AS THE HUMAN EYE!!
 - 1) Narrow loops or single straight line.
 - 2) Multiple loops, correct size, but with obvious "loopiness" to them. Fit line to the inspiratory limb of the relationship.
 - a) **TLC:** TLC should be recorded from each of the "linked" TGV-IC maneuvers or "linked" RV-inspiratory VC maneuvers during the continuous recording of lung volume. It should not be calculated from lung volume subdivisions taken from different maneuvers. Pick the 3 largest acceptable and reproducible TLCs obtained and calculate the mean of these 3 values.

(Reproducible means that the 2 smaller of the 3 TLCs are within 10% of the largest of the 3.) If there are only 2 acceptable and reproducible maneuvers, report the mean of the 2 largest acceptable and

reproducible values. If there is no acceptable and reproducible value, report largest acceptable TLC.

- b. **SVC:** Report largest acceptable SVC measured.
- c. **FRC(plethys):** The mean of the FRC(plethys) values associated with the maneuvers used for calculation of the mean TLC will be reported.

Clinics should follow their usual practice if the test session did not yield efforts that met the Lung HIV requirements. If the session, while not in conformance with the Lung HIV requirements, resulted in values which in the lab's usual practice would be considered reportable, the lab should report the obtained values but note on the report that the values did not meet Lung HIV requirements but are considered reportable (the note should specify which requirements were not met). If the session resulted in values which the lab would usually not consider reportable, then the values which did not meet Lung HIV requirements will be missing.

2. **Reported Values**

TLC, SVC, and FRC(plethys) are reported. RV will be calculated as reported (mean) TLC minus reported (maximum) SVC.

3. **Quality Control**

- a. The calibration of the flow, volume and pressure transducers should be performed in accordance with the manufacturer's specifications. This may require that the calibration be done with each test with the patient in the plethysmograph or may require that the calibration be done with the patient out of the box.
- b. Mouth pressure transducer and plethysmograph signal should be calibrated daily.

- c. Periodic (monthly) measurement of isothermal lung model to validate accuracy. Measurement should be within 50 mL or 3%, whichever is greater, based on a mean of five determinations.
- d. Normal subject repeated measures of two controls at monthly intervals or for trouble-shooting. Values should be within 10% for FRC and TLC, and within 20% for RV.
- e. Calibration records should be maintained and made available for review during site visits.

F. CT SCANNING

1. Participating Clinical Centers

The following clinical centers and sub-sites perform CT scans for Lung HIV participants:

Site 2 Johns Hopkins University Bloomberg School of Public Health

Johns Hopkins University School of Medicine

Site 4 Ohio State University

Site 7 University of Pittsburgh

University of California – Los Angeles

University of California – San Francisco

Site 8 Atlanta Veterans Affairs Medical Center

Bronx Veterans Affairs Medical Center

VA Greater Los Angeles Healthcare System

Completed scans will be shared on CD among the Clinical Centers performing CT procedures.

2. Schedule

The schedule for administering CT Scans will vary between Clinical Centers depending on the requirements of the individual protocols.

3. Specifications

Scanner						
Manufacturer	GE	GE	Siemens	Siemens	Philips	Philips
Model	LS 16	VCT	Sensation-16	Sensation-64	Brilliance-16	Brilliance-40
Acquisition						
Acquisition mode	Helical	Helical	Helical	Helical	Helical	Helical
Energy (kVp)	120	120	120	120	120	120
Tube current min-max (mA)	200-300	200-300	200-300	200-300	200-300	200-300
Tube current modulation	off	off	off	off	off	off
Gantry rotation time (sec)	0.5	0.5	0.5	0.5	0.5	0.5
Pitch	1.375	1.375	1.100	1.100	1.200	1.200
Detector collimation (mm)	0.625	0.625	0.750	0.600	0.750	0.625
Detector configuration (# detectors x mm)	16 x 0.625	64 x 0.625	16 x 0.750	64 x 0.600	16 x 0.750	40 x 0.625
Detector coverage (mm)	10.0	40.0	12.0	38.4	12.0	25.0
Table speed (mm/rot)	13.75	55.00	13.20	42.20	14.26	27.50
Breath-hold time for 280 mm (sec)	10.2	2.5	10.6	3.3	9.8	5.1
Breath-hold time for 400 mm (sec)	14.5	3.6	15.2	4.7	14.0	7.3
Reconstructions						
Reconstruction FOV will be set to completely encompass the lungs and as little of the chest as possible. Reconstruction matrix 512x512.						
Reconstruction 1						
Kernel	Bone	Bone	B46f	B46f	D	D
Image thickness (mm)	1.250	1.250	1.000	1.000	1.000	1.000
Interval (mm)	0.625	0.625	0.500	0.500	0.500	0.500
Reconstruction 2						
Kernel	Standard	Standard	B31f	B31f	B	B
Image thickness (mm)	1.250	1.250	1.000	1.000	1.000	1.000
Interval (mm)	0.625	0.625	0.500	0.500	0.500	0.500
Reconstruction 3						
Center can select third reconstruction to meet the needs of radiologist providing a clinical interpretation of the CT examination.						

4. Quality Assurance

Universal consistency of CT images will be ensured through the circulation of two identical phantoms among the above Lung HIV Clinical Centers. These Clinical Centers will perform CT scans on at least one Lung HIV phantom per quarter according to the current schedule posted on StudyCTMS.

Scanning of the phantom(s) will be performed according to the following procedures:

- a. Scan the phantom quarterly on each scanner used in the study.
- b. Scan the phantom as needed when there is a scanner change, x-ray tube change, or scanner software upgrade at a particular Clinical Center.
- c. Scan the phantom using the Lung-HIV protocol. If it is the first time scanning the phantom, also scan a standard water phantom. (All sites should have a water phantom for routine scanner calibration.)
- d. Copy the CT examinations of the phantom onto a DVD and ship to the evaluation center at the address below:

Ken Leader - Medical Department
University of Pittsburgh
Pulmonary Allergy - CCM Div.
3459 5th Avenue, NW
NW 628 Montefiore University Hospital
Pittsburgh, PA 15213

- e. Evaluate the phantom CT images to determine:
 - i. Mean and standard deviation of the computed attenuation (HU value) across the three foam inserts
 - ii. Measurement precision of simulated airways.
- f. Determine if the computed attenuation values are within an acceptable range. Notify the Coordinating Center if the values are outside an acceptable range.

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SPECIMEN COLLECTION PROCEDURES

A. Overview

An important objective of Lung HIV is to store biological specimens for future studies investigating the underlying pathogenesis of pulmonary complications associated with HIV infection. To this end, investigators in Lung HIV have agreed to process and ship blood and bronchoalveolar lavage (BAL) samples to a central repository at the National Heart Lung and Blood Institute (NHLBI). Only specimens collected as part of each center's main protocol will be sent to the central repository, provided enough sample is available for the primary protocol.

B. Specimen Collection

All subjects agreeing to have specimens stored in a central repository will provide informed consent. The consent will be "layered" so that subjects will be able to decide which specimens they agree to have stored and also whether or not they agree to genetic testing on the specimens. The planned specimens and potential future studies are outlined in the tables below. Blood specimens will be collected in an 8mL EDTA tube (purple top) and centrifuged so that packed cells, blood and plasma can be collected. Specimens will be prepared in aliquots as outlined in the tables below. The aliquots will be labeled (provided by the NHLBI) and stored locally at -80°C and then sent in batches to the NHLBI repository. Labels will have a BSI number that can be linked to relevant clinical data (e.g. pulmonary function, chest CT and respiratory symptoms/complications). Of note, the frequency of specimen collection may occur as often as every six months and will depend on the main protocol at the individual center. The separation of blood into packed cells and plasma will provide the simplest route to future genetic studies and protein assays. Detailed information is provided in the following sections of this manual:

- Appendix F – Repository Concept Sheet

- Appendix G – Specimen Collection Plan
- Appendix H – Common Specimen Collection and Processing Protocol (Blood Products)
- Appendix I – Common Specimen Collection and Processing Protocol (BAL) (Site-specific specimen protocols and procedures can be found under the respective Clinical Site appendices in the Common Protocol.)

In a similar fashion, BAL fluid will be collected at varying time intervals throughout the course of the Lung HIV Study. Centers have agreed to donate any BAL fluid remaining after fulfillment of their local protocol. Centers will process BAL fluid, locally store BAL supernatant and cell aliquots at -80°C, and send in batches to the NHLBI Repository.

Of note, there will be considerable variation among the clinical centers performing BAL with respect to the timing and clinical conditions surrounding bronchoscopy (e.g. medical condition of subject, volumes used, lobe lavaged, etc.).

C. Obtaining Stored Specimens

The process involved in requesting biospecimens from the Repository is determined by the “Proprietary Period” or “Open Period” status of the study collection. The “Proprietary Period” lasts until the clinical study data are made available for sharing following the NHLBI Limited Access Data Sharing Policy timeline. During the “Proprietary Period,” only centers involved in Lung HIV will be permitted access to the specimens. During the “Open Period,” specimens will be available to all investigators successfully completing the application process as described below.

Investigators will need to provide a design of the proposed research and evidence of the qualification to perform the research. In addition, evidence of the availability of funding to perform the requested research must also be provided. Furthermore, investigators wishing to obtain specimens must address ethical and legal considerations, including consistency with the terms of the informed consent and compliance with human subjects and HIPAA regulations.

Investigators requesting biospecimens during the “Proprietary Period” will need permission of the HIV Lung Steering Committee prior to release of specimens to the investigator.

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ADVERSE EVENT REPORTING PROCEDURE

A. Overview

The Lung HIV DSMB will be informed of all Adverse Events (AEs) that are possibly, probably, or definitely related to Lung HIV Study interventions or procedures, provided such events are either:

- Serious Adverse Events (SAEs)
- or
- Unexpected Adverse Events (UAE)

B. Reporting Procedure

When an SAE or UAE is identified at any Lung HIV Clinical Site, the Lung HIV Data Coordinating Center (C-TASC) must be notified as soon as possible. The nature of such notification will vary according to the manner in which the respective Clinical Site is collecting Lung HIV Study data in StudyCTMS:

- Direct data entry

At some Lung HIV Clinical Sites, study data are entered directly into StudyCTMS. At these locations, submission of an electronic Adverse Event Form (Common Form 000-012) triggers an automatic email which notifies the Lung HIV project team at C-TASC that an event has occurred.

- Data uploads

At some Lung HIV Clinical Sites, study data are uploaded into StudyCTMS at regular time intervals. When an event is identified at these locations, a handwritten Adverse Event Form (Common Form 000-012) must be completed and forwarded to C-TASC by either of the following methods:

- Fax to 410-435-0689 (Attention: Lung HIV Study Manager)
- Email of an electronic document (scan, PDF, etc.) to the Lung HIV Study Manager.
- Data submission pending

At a few Lung HIV Clinical Sites, study data are not yet being submitted into StudyCTMS. Until data entry and/or upload functionality is finalized for these projects, Adverse Events at these locations should be reported to the DCC according to the “Data uploads” section above.

C. Documentation Requirements

For **all** events, regardless of notification method, supporting documentation must be forwarded to C-TASC via fax or email within 72 hours following the date on which the Data Coordinating Center became aware of the event. Within seven days, the C-TASC project team will prepare a formal submission packet and submit it to the Lung HIV DSMB. C-TASC will then facilitate communication between the DSMB Members and the respective Clinical Site PI to resolve any questions or concerns that may arise.

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CHAPTER 7

COMPLETION OF DATA COLLECTION FORMS

A. IDENTIFICATION NUMBERS AND CODES

1. General Guidelines

Each form has certain key items at the top which uniquely identify that form. These items must be filled in on all forms. These items are the patient's Identification (ID) Number, letter code, form type and the date of the examination or procedure. If this information is not completed correctly, the form cannot be processed by the DCC.

Each subject is assigned a unique Identification Number by the Study Coordinator at the time the subject is enrolled. This ID Number consists of eight digits; the first three digits represent the Clinical Center number (assigned by the DCC before patient enrollment begins), the next four digits identify the subject, and the last digit is a check digit. The DCC will provide a list of ID numbers and letter codes to each Clinical Center. The study coordinator should use each ID number once, in the order given on this list.

Once an ID number and letter code are assigned and keyed for the first time, they cannot be changed. The letter code and ID Number must be used on all of a subject's Lung HIV Study forms and correspondence.

2. Clinic ID

The DCC has assigned the following Clinical Center ID numbers:

001 – Johns Hopkins University – Medical

002 – Johns Hopkins University – Bloomberg School of Public Health

004 – Ohio State University

005 – University of California, San Francisco

006 – University of Colorado Health Sciences Center

007 – University of Pittsburgh

008 –University of Washington

This three-digit code comprises the first three digits of the ID number.

3. Patient ID

At each clinical center, the study coordinator will identify a subject by a unique four-digit number, beginning at 0001 and proceeding in order until recruitment is complete. This four digit code comprises the fourth through eighth digits of the ID number.

4. Check Digit

This single digit will be supplied by the DCC as a method to ensure the proper ID has been keyed. This number comprises the last digit of the ID number.

5. Letter Code

A three-character letter code will be supplied by the DCC as a second check to ensure the proper ID number has been keyed. This is a random code and will not contain any patient identifiers.

6. Specimen ID

Each laboratory specimen will be labeled by a six-digit specimen ID number which is independent of the ID number. The first five digits will be randomly generated and the sixth digit is a check digit. These specimen ID numbers will be generated by the DCC.

7. Staff Number

These numbers are assigned by the DCC for each Clinical Center staff member who has been certified to perform Lung HIV Study procedures. This number will be recorded in the “Administrative Matters” section at the end of each Lung HIV Study form.

B. COMPLETING FORMS

1. General Guidelines

There are three types of Lung HIV Study Forms: (1) forms which are completed and retained at the Clinical Center and are not sent to the DCC. These are for the Clinical Center's internal use only and should be filed in the patient record; (2) forms which are designed to be transmitted from the Clinical Center to the Data Coordinating Center by Internet Data Entry; (3) Forms or manifests detailing the contents of a package sent to a Core Laboratory which accompany each shipment. These forms should be completed and data entered by the Study Coordinator. A manifest is generated to be included in the package. The manifest will be reviewed by Core Laboratory staff upon receipt. The manifest will contain only specimen numbers, no patient identifiers.

The underlying principle in processing information in the DCC is to process the information as submitted without interpretation or second guessing what the recorder had intended. The providers of the data are requested to complete the forms as clearly and as legibly as possible, but also to follow certain conventions in reporting data to reduce the possibility of errors in processing the data collection forms.

Before keying into the data entry system, each form should be reviewed for completeness and accuracy. The person who collected the information is responsible for its accuracy, and he/she documents this by signing the form and providing his/her staff certification number (assigned by the DCC). All completed forms should be filed in the subject's Lung HIV Study records at the Clinical Center.

2. Obtaining Study Forms

Copies of the Lung HIV Study forms can be obtained from the "Forms" section of the Lung HIV Study Web Site and using Adobe Acrobat Reader to print the required forms. Only the current version of a form will be posted. If a form revision is made, a numbered memo will

be distributed detailing the change(s) made. Any unused copies of the prior form version should be destroyed. The revised form should be used at all subsequent study visits.

3. Dates

As part of the identifying information a date is required. The appropriate date is the date of the study visit. All dates on Lung HIV Study Forms are to be recorded as a three-letter abbreviation of the month (first three letters), a two-digit date (a leading zero is to be used for dates 1-9), and the complete four-digit year. The following letters are to be used for each month: January = JAN, February = FEB, March = MAR, April = APR, May = MAY, June = JUN, July = JUL, August = AUG, September = SEP, October = OCT, November = NOV, December = DEC. Thus, June 1, 1999 would be JUN-01-1999 and November 10, 2000 would be NOV-10-2000.

4. Completing Form Items

Pre-coded multiple choice items should be selected by clearly circling or checking the appropriate number. Only one choice should be indicated.

Numeric items should be right justified and leading zeros should be recorded in spaces not used. For example, if the item has three spaces and the number "12" needs to be entered.

Response is "12" → 0 1 2

Alphabetic write-ins are often used for comments or specifying "other" responses. Write clearly, starting on the far left of the line(s) provided.

All form items are to be completed in blue or black, non-erasable ink. Pencil or "white out" should not be used.

5. Missing Data

Provide all available data. This will prevent unnecessary edit queries. Some items may be left blank if there is a conditional skip (e.g., if ..., then skip to ...). Certain form items have choices for the response "unknown" or "uncertain" or "not available." These responses may be used if the information is not available.

6. Correcting Form Items

If it is necessary to correct or change a form item, completely cross out the incorrect response and indicate the new response. The staff member making the change must place the date the change was made and their initials in ink next to the correct response. Do not use “white-out,” correction tape or pencil to make corrections.

If the form had already been keyed, this correction will also need to be made in the data entry system (see Chapter 9).

7. Administrative Sign-Off

Each Lung HIV Study form will require at least one Lung HIV staff member signature (Study Coordinator) in the “Administrative Matters” section at the end of the form. Depending on the form, the signature of the Principal Investigator, Co-Investigator or technician may also be required. All forms should contain the required signature prior to data entry.

C. HANDLING FORMS

1. Duplication

All Lung HIV Study forms will be posted on the Lung HIV Study web page under “Forms.” Optimally, Forms should be printed out as needed from the web page to ensure the most recent version is being used. However, duplication of a form may be efficacious at times.

It is expected that some forms will need to be revised during the Lung HIV Study. DO NOT photocopy huge quantities at one time. If a form is revised, all copies of the old version of the form should be immediately destroyed to prevent their accidental use.

2. Storage

Each patient randomized in Lung HIV Study will have an individual patient file folder or notebook which is to be kept in a locked room or locked filing cabinet. The patient file or notebook should contain all the forms completed for the patient and related Lung HIV Study documents specific to the patient (e.g., consent statements). The forms should be arranged in

the file or notebook in form order. Screening, randomization and shipping materials, such as labels, will also be stored in the patient file or notebook.

D. DATA ROUNDING RULE

To round data, examine the digits following the last data position required on the form:

- If the first digit following the last data position required for the response is less than 5, leave the digit in the last data position required for the response unchanged, e.g., if you need to round to __.__, then 4.73 rounds to 4.7 and 1.44 rounds to 1.4
- If the first digit following the last data position required for the response is 5 or more, round up the digit in the last data position required for the response, e.g., if you need to round __.__, then 4.78 rounds to 4.8 and 4.75 rounds to 4.8

When completing a calculation for Lung HIV Study, apply the rounding rule only when required to record a quantity on the Lung HIV Study form.

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INSTRUCTIONS FOR USE OF LUNG HIV STUDY WEB SITE

A. OVERVIEW

The Lung HIV Study Web Site is available for use by all Lung HIV Study Clinical Center, Project Office, and Core Laboratory staff. For questions about the Web Site, contact the Lung HIV Study Coordinator or Programmer at the DCC.

To access the Lung HIV Study Web Site type <http://www.lunghiv.com> into your browser's address window. Most documents available on the Lung HIV Study Web Site are in Portable Document Format (PDF). Documents in PDF preserve the exact look and content of the originals. Adobe Acrobat Reader 4.0 or higher is required to read and print the PDF documents. This product is free and is available from Adobe at <http://www.adobe.com/products/acrobat/readstep.html>. There is a link to Adobe on each of the Lung HIV Study Web Site pages. When installing the program from the Adobe Web Site, follow the directions given on that Web Site. Click on the file name to open a PDF document with the Adobe Acrobat Reader.

B. CONTENTS OF THE LUNG HIV STUDY WEB SITE

The Lung HIV Study Home Page (Appendix C) identifies the categories of information available on the Web Site and provides links to those sections. To review the contents of each section, click on the section heading. The page for that section is then displayed. Each page lists the documents available in that section for the given category. The list can be quite long. To aid in finding documents in a section, a drop down list is provided to limit the list of documents to a smaller subset of that category.

C. SYSTEM REQUIREMENTS TO ACCESS THE LUNG HIV WEB SITE

In order to use the Web Site, a staff member must have a computer with the following configuration.

1. High speed internet connection
2. Pentium Class PC running Windows 98, Windows NT, Windows 2000, Windows XP, or more recent versions of Windows.

3. Microsoft Internet Explorer 5.5 or greater or Netscape 4.7 or greater.

The browser must be set to accept cookies

NOTE: The faster the machine and the more memory available, the faster the data entry system will respond.

D. PRINTING STUDY FORMS OR OTHER DOCUMENTS ON THE LUNG HIV WEB SITE

Study forms are available through the Lung HIV electronic data capture system (StudyCTMS). A link on the left side of the Lung HIV study website will take display a log-on screen where a username and password is required. Detailed instructions are provided in the Lung HIV Users Guide (Appendix D). A list of Lung HIV study forms is provided in Appendix E.

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CHAPTER 9

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CHAPTER 9

MONITORING STUDY PROGRESS AND DATA QUALITY

A. INTRODUCTION

This plan describes how the DCC fulfills the study's protocol expectations for investigative site monitoring by a Clinical Research Associate (CRA), including the preparation and follow-up activities.

The primary concerns of the DCC's Clinical Research Associate and affiliated staff members will be to ensure the safety and confidentiality of enrolled study participants; confirm the study team's adherence to the current protocol and ICH/GCP guidelines; and confirm the accuracy and completeness of the data collected at the investigational research site.

Three major steps are associated with ensuring the safety and confidentiality of each enrolled study participant: 1) Review and confirm the investigative facility's Institutional review Board (IRB) approval(s) of the study specific Informed Consent Form (ICF); 2) Review and confirm that all enrolled study participants had the opportunity to review; ask questions; and were provided a copy of their signed ICF (w/HIPPA statement) prior to the completion of any study related procedures; 3) Ensure all patient related study materials are securely stored, retrievable, and protected against unforeseen circumstances (e.g. natural / man-made disaster).

Three major steps are associated with ensuring the site's adherence to the current protocol and GCP guidelines which are: 1) Review and share with the site staff findings from the DCC's source data verification of 5 - 10 % of the site's captured data; 2) Review and share with the site staff findings from the DCC's running of a site specific 'Visit Schedule Report' documenting the enrolled patient's expected clinic visit range; 3) Review and share with the site staff findings from the site-specific StudyCTMS history report. This report outlines the site's total number of completed FORMS (common and site specific), as well as those FORMS that are "Failing Edit".

There are two major steps associated with ensuring that accurate and complete data will be collected: 1) All persons associated with data collection should have documented study

specific training (with a refresher provided as needed) to familiarized them with the tasks they are to perform as noted in

the current protocol; 2) All persons associated with data collection and entry should have properly documented StudyCTMS training with a user's certification properly awarded prior to performing any study data entry.

Monitoring reports regarding the investigative facility's performance in the areas of patient recruitment/retention; Protocol adherence, and performance/execution of study related procedures will be prepared following each site visit.

The monitoring report should be prepared within 2-weeks of the CRA's visit to the investigative site. Once the monitoring report is completed, it should initially be reviewed by the Lung HIV Principal Investigator (Bruce Thompson, Ph.D.) for comments. Afterwards, the final report should be submitted to the investigative site' Principal Investigator (PI) and the NHLBI Project Officer within three weekend of the site visit.

B. Patient Tracking and Deactivation Log

The DCC has designed multiple Excel spreadsheets to be used to record study data, such as the forms each active patient should complete at each designated clinic visit; another one that notes the CT scans collected at the designated clinic visit; and a final one that documents the study related Serious Adverse Events (SAEs) and their outcomes as captured at each Investigative site. No personal health information will be included in these logs.

These spreadsheets are maintained by the DCC to tabulate the total number of subjects screened for the Lung HIV Study.

C. Periodic QA Reporting

The DCC will prepare a monthly 'Performance and Data Quality' reports. These reports will reflect the status of all data received at the DCC since the last day of the preceding month and will be distributed to the Steering Committee prior to the second Thursday of each month (date of monthly Steering Committee meetings). All reports will be posted in the StudyCTMS.

These reports will contain the following:

- Total number of FORMS received from the sites (per site)
- FORMS received from the sites in the past 4-weeks (per site)
- Total number of FORMS edited and were found to be passing edit (per site)

In addition to the DCC's 'Performance and Data Quality' Report, on a semi-annual basis a 'Protocol Summary' Report should be updates each investigative site. The 'Protocol Summary' reports reflect the status of all data received at the DCC since the last day of the preceding month and will be distributed to the Data Safety Management Board (DSMB) at the spring and fall meetings. All reports will be posted in the StudyCTMS in the 'Documents' module.

These reports will contain the following:

- Project Description and/or Objectives
- 'Underlying Population/Cohorts'
- 'Summary of Project Structure'
- Patient 'Enrollment Status'
- Sites Location (s)
- Current Issues with the IRB
- Protocol Version Information
- Informed Consent Form Status Updates
- FORM data entry method (data entry /upload) and items to be added to the patients data set
- Notification of any new SAE that occurred since the previous site visit.
- A list of the site's projected Bio-Repository Contribution(s)
 - Summary of Specimen Collection Status
- Outstanding Action Items from Last Review

D. Quality Monitoring

The DCC staff will review an arbitrary sample of completed study forms (common and site specific) to ensure that only certified site study staff are performing only study related procedures, processes and management, of data found in the DCC 's StudyCTMS.

The NHLBI Project Officer will be notified if one or more participating investigative site has greater than 10% of their expected forms delinquent or failing edit or other problems (e.g., more than 2% data entry errors).

If necessary, Steering Committee members will conduct a special site visit to provide assistance to resolve the problems.

During the site monitoring visit, the CRA will compare a sample of the computerized study data forms as found in the DCC's StudyCTMS against original patient records. Any discrepancies are documented and adjudicated by the DCC-CRA and all documented findings will be immediately communicated to the investigative site coordinator for resolution.

Reports of these special visits will be submitted to the DSMB along with any recommendation(s) to the Steering Committee concerning continued participation of the investigative site. The documented findings regarding any individual sites are summarized in the semi-annual performance reports.

E. Site Visits

This study will not require site visits to monitor the common protocol. This section will remain blank as recommended by the Lung HIV DSMB.

5. Data Management Activities

Procedures for data entry / edits are reviewed, as well as the procedures for filing records. For the Lung HIV Study, this portion of the site visit is for the review of documented site request submitted to the DCC for data forms changes /modifications /deletions. The site's request is examined to determine that the appropriate procedures for making corrections on the study forms have been followed.

The Site Monitoring Report will be prepared within two weeks of the visit and distributed to the site visit team. The final report should be submitted to the investigative site's Principal Investigator and the NHLBI Project Officer within three weeks of the visit.

The PI will be requested to respond to the CRA's reported findings as noted in the visit report within two weeks of his/her receipt of this document. In the PI's responses, it is expected to see a summary of corrective measures the site will employ to address the findings as noted by the CRA.

F. Data Coordinating Center (DCC) Activities

To test the development of the data entry and edit system, study forms will be completed with deliberate errors. These forms are then processed through the StudyCTMS to determine that variables are correctly mapped from the form to the database and to determine that the errors were detected.

A sample of data items from patient forms that have been entered on the DCC database will be compared to the copy of the source. The results are then used to assess the reliability of the site's data entry process. Problems with low reliability for data entry of any item will be resolved. (Note: No audits of site protocol specific data will be conducted,...only for data common to the Lung HIV Study's objectives will be outlined for data review and monitoring)

Note: Any primary outcome analysis for a manuscript will be replicated independently by two biostatisticians or statistical programmers to reduce the possibility that there are programming errors producing incorrect results.

G. Editing Data

Items on the data collection forms are sometimes overlooked, information is sometimes recorded incorrectly, or items are answered inconsistently. In order to identify such problems and to retrieve as much information as possible, all forms are computer edited to detect missing or improbable answers to every item during the data entry.

Problems detected by the StudyCTMS edit package will generate 'Failing Edit' status that is associated with form's embedded consistency statements. The investigative site should contact the CRA in writing (E-mail) to resolve any edit-related messages of uncertainty. A

description of edit procedures and the routine procedures for dealing with edit messages follows.

H. Encountering Data Entry Errors

In common usage, an error is a mistake, perhaps a “typo.” These errors can occur during transcription and must be addressed. However, in StudyCTMS, an “error” is a technical term that refers to the following errors, alert symbols, and captions:

- **Out-of-Range Data Error:**

An out-of-range error results from a numeric entry found to be outside the limits programmed into the field. There are three types of data limits:

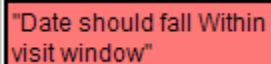
Data—The outer limit of possible answers using mathematical, time or other parameters. These limits cannot be overridden by the data entry user. *Example:* If the maximum number of hours in a day for time purposes is 23, an error occurs when the user enters 28.

Study—The limit imposed by study requirements. A study range limit can be overridden by the user with permission to do so. *Example:* If a date for a visit occurs outside the specified window, an error is detected (as pictured in the alert caption below).

Human—The realistic range for such measurements as age, height, and weight. A human range limit can be overridden by the user with permissions to do so.

Symbol:  [Alert]

Caption (Sample):



"Date should fall Within
visit window"

- **Consistency Error:**

A consistency error means that at least one of at least two related answers is not consistent with another answer. *Example:* A consistency error occurs if ‘No’ was checked in response to a question asking if an X-ray was taken, yet a subsequent answer displays an X-ray result of Negative.

The system may also find a consistency error when data entered does not match corresponding data found elsewhere in the database, such as an incorrect Certification Number.

Symbol:  [Consistency]

Caption: Provides specific information on the nature of the inconsistency.

- **Omission/Required Field not Completed:**

When a field that is required has not been keyed, an alert appears, also designated by an

Symbol:  [Alert]

Caption: 

- **“Skip” Prompt and Programming Option**

Forms are often made up of “branches.” Each branch is comprised of a series of questions whose relevance is dependent on the answer to a primary question. If the secondary questions are no longer applicable, the form advises the user about where to proceed next.

This process is called “skip logic.”

Example: As the prompt below indicates, if ‘No’ is the response to the first question in Section A, the user “skips” the remainder of the section and proceeds directly to Section B:

IF NO, SKIP TO SECTION B

(Option) Where programmed to do so, StudyCTMS applies skip logic to *automatically* move the user to the next relevant data-entry section.

I. Delinquent Listings

Via StudyCTMS options, a user has the ability to view the site’s inventory of completed forms as a comparison to the forms that are expected. Forms are listed as delinquent if the form in question has not been completed within the visit window as established in

the 'Visit Schedule Report'. (Note: An opened form must be in the 'Passing Edit' status to prevent being displayed as a delinquent document.)

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Appendix A

Lung HIV Home Page

The screenshot shows a web browser window displaying the Lung HIV Home Page. The browser's address bar is empty, and the status bar at the bottom shows "Done" and "Internet". The page features a blue header with the Lung HIV logo and the text "an NHLBI sponsored cooperative project". A navigation menu on the left includes links for Home, History, Abstracts, Publications, Study Roster, Committees, Latest News, StudyCTMS, and Contact Us. The main content area has a large image of a cliffside overlooking the ocean, with the text "Lung HIV Study" overlaid. Below the image, the text reads: "The Lung HIV Study", "Longitudinal Studies of HIV-Associated Lung Infections and Complications (Lung HIV)", and "RFA HL07-00S". A paragraph of text follows, describing the study's collaborative nature and goals. The page concludes with a paragraph about the Lung HIV mission.

LUNG HIV
an NHLBI sponsored
cooperative project

Home
History
Abstracts
Publications
Study Roster
Committees
Latest News
StudyCTMS
Contact Us

Lung HIV Study

The Lung HIV Study
Longitudinal Studies of HIV-Associated Lung Infections and Complications (Lung HIV)
RFA HL07-00S

Lung HIV is a collaborative multi-site study sponsored by [the National Heart, Lung, and Blood Institute \(NHLBI\)](#) to examine a broad range of separate yet overlapping pulmonary topics. Eight Clinical Centers and a Data Coordinating Center have been tasked with creating a collection of datasets and biological specimens for use during this RFA and in future investigations. The program is structured to facilitate both the development of these shared resources and the completion of the individual projects. Results of these efforts will be disseminated through publication in leading medical journals.

The Lung HIV mission is to achieve a clear understanding of the clinical manifestations of HIV-associated pulmonary complications by fostering multidisciplinary research collaboration and establishing a high quality centralized specimen repository with an associated clinical dataset based on shared definitions.

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Appendix B

Study CTMS Users Guide



Clinical Trials & Surveys Corp.

User Instructions



For StudyCTMS

Web-based Clinical Trials Management System

Version 1.0.1



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StudyCTMS Use Instructions

Introduction

StudyCTMS is a suite of software tools developed by Clinical Trials & Surveys Corp. (CTASC) to provide a real-time online community for study staff. Within it users can find key study information, manage study documents, discuss key topics, enter data into study forms, edit and validate study data, run statistical analyses and view reports.

This document provides detailed instructions on the use of all areas available in the StudyCTMS application. Not all users will have access to all features discussed in this guide.

Instructions for Systems Administration may be found in a separate document titled StudyCTMS Systems Administration Instructions.

Access

To access StudyCTMS click on the following link or enter <https://www.studyctms.com> into your browser. Note all access utilizes HTTPS/SSL 128-bit encryption and requires a valid username and password. For users with access to more than one study, a Select Study field will appear. Users with access to only one study will not see this field.

In case of a forgotten password, use the “Forgot your password?” link. This will reset your password and send a new password to your registered email address.

Navigation

The Navigation of StudyCTMS will change based on the user rights. The system has three major points of navigation, top tabs, tab links and quick links. Hovering over a top tab will display all tab links associated with that tab. Users will see only those tabs allowed by their user rights. This provides security while also simplifying the user interface to show only those features each user really needs access to.

Tab Menu

The Tab menu begins with a home page containing the user’s dashboard then provides tabs that contain features for Visit data entry, Form Validation and Data Analysis.



Tab Links

When a user hovers over any tab the list of features offered within that tab are displayed. Any of these links may be clicked to launch that application feature. Links are only shown while the user hovers over the appropriate tab.



Home Documents Discussions

HOME VISIT VALIDATE ANALYZE

Quick Links

The Quick Links menu contains one-click features related to system maintenance and use including links that allow users to change their password, logout of the system, launch the Help document and, for Systems Administrators, provides access to the Administration Dashboard.

[Change Password](#) | [Administration](#) | [Logout](#) | [Help](#)

HOME

Home Tab

Home Page

The Home page contains basic information about the study often with the ability to drill into more detail on key study information. It also contains a one-click Action panel that contains a User personalized list of common actions.

In the 1.0 release of the application, the contents of the User dashboard are fixed and include: Study News, Upcoming Site Visits, Study Links, My Weather and the Action Panel. In an upcoming release, several additional dashboard objects will be added as well as the ability for users to personalize this view.

The **Study News** object provides an area for the Study Manager, DCC, PI or other study members to disseminate information about the study. This may include hyperlinks to any URL. All users will have access to this object.

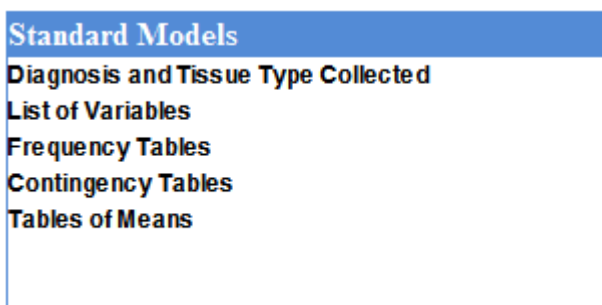
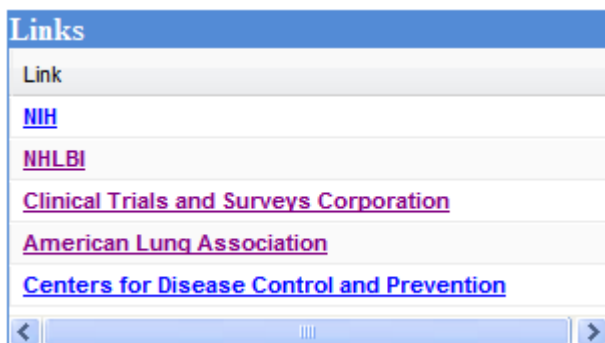
Study News	
Date	News Item
FEB-08-2008	Welcome to StudyCTMS.com for the LUNG HIV Study! This site is provided to all study participants by the National Heart, Lung, and Blood Institute (NHLBI) and Clinical Trials & Surveys Corp.(C-TASC) .
FEB-08-2008	Please send question, compliments or concerns to webmaster@c-tasc.com

The **Upcoming Site Visits** object provides a chronological view of site visits scheduled to occur in the coming months. This object will be empty for the early stages a study.

Upcoming Site Visits			
Visit Date	Site	City	State
SEP-24-2007	University of Pittsburgh	Pittsburg	PA
OCT-02-2007	Radiology Core Lab	Rochester	MN
OCT-03-2007	Mayo Clinic - Rochester	Rochester	MN
OCT-17-2007	University of Michigan	Ann Arbor	MI
NOV-13-2007	Tissue Core Lab	Denver	CO
NOV-14-2007	University of Colorado	Denver	CO



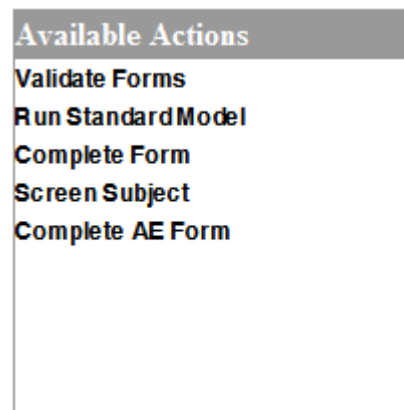
The **Links** object includes links to external sites related to the study. Links can be added by Systems Administrators based on user requests. Clicking on any link will launch a new browser window which will load the site clicked.



The **Standard Model** object provides one-click access to statistical models delivered with the software. These models are pre-configured SAS programs which run within StudyCTMS using integration with SAS IntrNet. Only users that have access to the Standard Models link under the Analyze tab will see this object.

The **Action Panel** is intended to provide a place for the user to setup one-click links to parts of the system that they use often. Different users will have access to different Actions based on their user role. At the early stage of a study users may not see the Action Panel as most Actions are tied to features used during data collection and analysis. Clicking on any action will immediately bring the user to the function selected.

New Actions will be added with every release of the software.



Documents

The Documents feature provides users with the ability to setup folders, upload documents, check-out documents for editing and view documents.


All users will see the study folder which will always be listed at the top. A folder to represent each study site will be available underneath the study folder. Only users associated with any given site will see that site's folder and sub-folders.

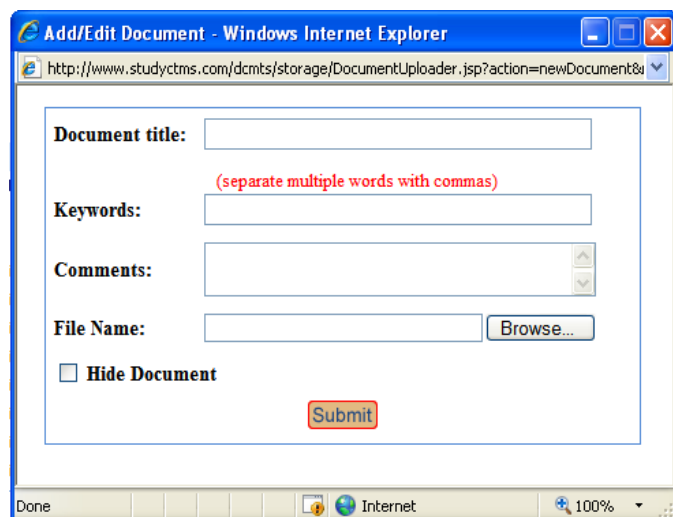
Viewing a document

To view any document, first navigate to it by opening any and all folders required until you find the document. Double-clicking on the document you wish to view will cause that document to pop-up in a new browser window. Depending on the native format of

the document you are viewing, the browser may contain a limited set of features from that application. For example, if a Microsoft Word document is opened, you will see print, save and basic formatting features from MS Word within the browser. When you are done reviewing the document simply close the browser window.

Uploading a new document

To upload a new document, first navigate to the folder into which you wish to load the document. Next click on the  icon. Doing this will launch the Add/Edit Document pop-up. This pop-up will collect a small set of data about the document including:



- Document Title – this is the name that will appear in the document folder list
- Keywords – one or more words, separated by commas, that can be used in a document keyword search
- Comments – up to 255 characters of detailed description or comments about the document
- File Name – Use the **Browse** button to locate any document that your local PC has access to then click on it, loading that file's name into this field.
- Hide Document – can be checked if the user would like to upload


a document but hide it from all other users. If this box is checked, only the user that uploaded the document will see the document in the folder list.

The Document Title and valid File Name are the only required fields on this page. Once you are done entering document information click Submit. The file will then be uploaded to the system into the folder selected.


NOTE: the period of time it takes to upload a document depends on the size of the file and the speed of an individual user's Internet connection, not the speed of C-TASC's servers. Please compress large files and/or upload using a broadband connection

Uploading a revision

To upload a revision of any document, first navigate to the document you would like to update and single click on it. Note the Document Status listed on the far right. If you have not previously check-out the document you may not upload a revision. Go to ["Checking out and downloading a document"](#) to check out the document.


Once you have check-out the document, to upload a revision, click on the  icon which will pop-up an empty Add/Edit Document window identical to the box that appears when uploading a new document. Enter data as desired making sure to include at least a Document Title and File Name (required fields). When done, click Submit to upload the document.

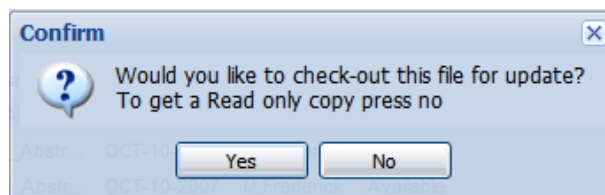
Editing Document Information

When a document is uploaded a small set of data about that document is collected (see above). To edit this information first navigate to the document. Next click on the  icon. This will launch the Add/Edit Document pop-up with all existing document information pre-loaded, with the exception of the File Name, which can not be altered. Simply edit any fields you would like and click Submit when done.

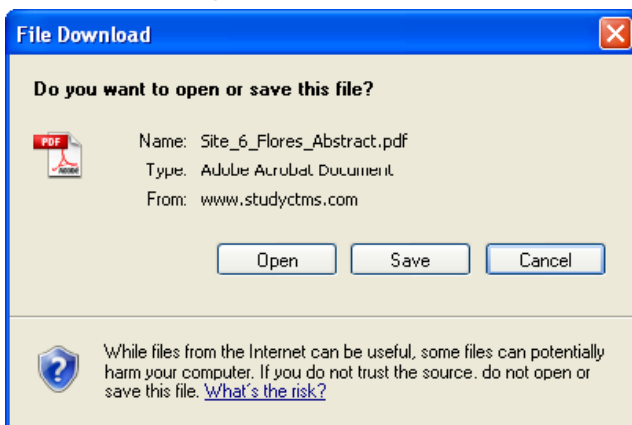
Checking out and downloading a document

Before any document can be edited it must first be checked out. This feature ensures that no more than one person can be editing the same version of any document at the same time causing merge problems at a later date.

To check out any document first navigate to the document and single click on it. Next, click on the  icon. The screen will then gray out and a message box will appear asking whether you would like to check out the document. Click "Yes" to check out the document and click "No" to see a read only version of the document.




In either case you will then receive the standard Windows message box asking if you would like to Open or Save the document or Cancel the transaction. If you do NOT see this box you likely have a pop-up blocker or other security software that is disallowing the download. Look at the top of the screen immediately under the browser header for a permission bar. Right click on this and select the option that allows you to download the file. You should only have to do this one after each time you log in.




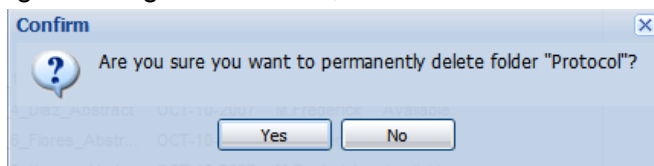
laptop as long as you have an application registered to read the type of file you have downloaded.

Adding a folder

Any user with edit rights to the Document section of StudyCTMS may add or edit folders. To add a folder first navigate to a parent folder under which you would like to add the new folder and click on that parent folder. Any folder at any level may serve as a parent to a new sub-folder. Next, click on the  icon which will cause the add/edit folder pop-up to appear. This pop-up contains only one field, "Folder Name". Enter any combination of text, spaces and numbers as a folder name then click Submit. As soon as Submit is clicked the pop-up box will disappear and the folder will appear on the main Document screen.

Deleting a folder

Any user with delete rights to the Document section of StudyCTMS may delete an existing folder. To delete a folder navigate to the folder you would like to delete and click on it. The folder will now appear highlighted in light blue. Next, click the  icon. This will launch a confirmation message box making sure you want to permanently delete the folder. Click “Yes” to delete the folder and “No” to return to the document list without deleting the folder.



Discussion Forums

The Discussion Forums feature of StudyCTMS has been provided to enable online collaboration amongst study staff. Within this area of the product users may review postings, add a posting to forums, respond to prior postings, print a posting, delete postings they have added, see who is online, track their favorite discussions (threads), search discussions for specific user posts or topics, view their profile, send private messages to any internal or external user or review messages received.

Navigation

[Index](#) | [Recent Threads](#) | [Who's Online](#) | [My Profile](#) | [Search](#)

Due to the large amount of functionality within the Discussion Forums area, an additional menu bar has been included. This provides a way for users to easily navigate around this area of the application. The menu bar includes five links:

- [Index](#) – the Discussion Forum dashboard
- [Recent Threads](#) – a list of threads added in the last 24 hours
- [Who's Online](#) – a list of users who are currently online in any part of the application
- [My Profile](#) – A view of the user's profile information as recorded by the system
- [Search](#) – access to a search engine that allows the user to search through all discussion forums.

Index

When arriving at the Discussion Forums area of the software, the user will arrive at a Forum dashboard. This includes a list of users online, a list of all available forums and a list of last posting in each forum.

Viewing available Forums

On the bottom left of the Discussion Forum dashboard is a list of all available forums for the study. You will only see those forums that your user group has rights to. All Forums are study-specific so if you have multi-study rights you will only be able to see the forums for the study you have logged into.

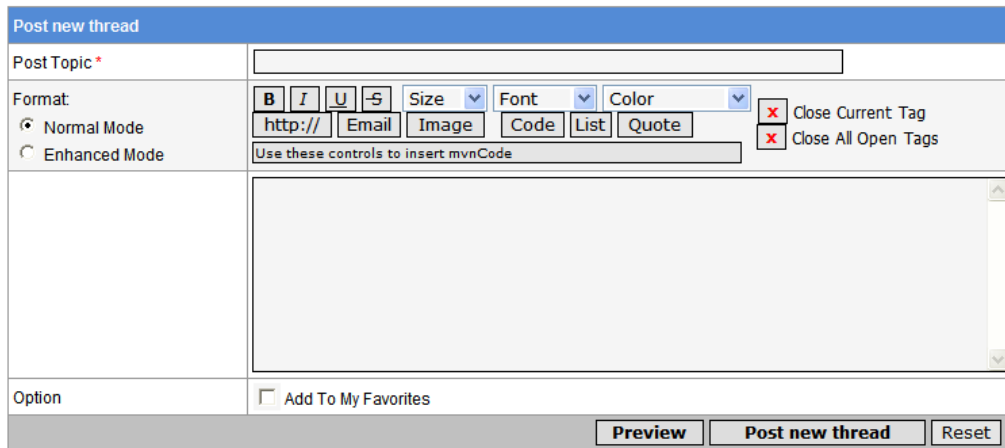
To view the contents of that forum simply click on the forum name.

List all forums
Document Discussion ▾
General Discussion
Informatics Committee
Respository Committee
PFT Committee
CT Scans Committee
Diagnoses Committee
Laboratory Measures Committee
Questionnaires Committee

NOTE: adding a new Discussion Forum requires special system permissions. If you would like to add a new forum, please contact your Systems Administrator

Post a New Thread

Once you are in a Discussion Forum, you will see a link “Post a new Thread” on the bottom right and top right of the Forum posting list. To add a new thread click one of these links. This action will take you to a thread editor that functions like a simple version of MS Word.



First enter a Post topic and then enter text into the large open text area. Use the Format buttons to add bold, italics, underline or strikeouts to text or to change text font, size or color. You can also use available buttons to add a URL (http:// button), an email address, an image, HTML code, a numbered or lettered list (list button), or to add a pre-formatted quote. If you are familiar with HTML you can also type HTML code directly into the text area or paste it in from an external HTML editor.

Once you have finished entering the post text and formatting, you may click **Preview** to review your post before submitting it, or **Post new thread** to post the thread immediately. When you have posted your thread you will be returned to the Discussion Forum main page which will now display your new post.

Viewing posts

Within any forum all posts will be listed. There are two types of posts: a thread and a reply. A thread is the beginning of a discussion and will be shown in orange above all replies to the thread. Any thread may have any number of replies which are listed in white below the thread in the order posted.

Total posts in this thread: 2 [\[Add To My Favorites\]](#) [\[Watch this Thread\]](#) [\[Post new Thread\]](#)

Author	This topic has been viewed 1 times and has 1 reply	
ivaleri@ctasc.com Joined: Dec 19, 2007 Posts: 1 Status: Online	Welcome to the Lung HIV Discussion Board! <div style="text-align: center; font-size: 2em; font-weight: bold; color: red;">THREAD</div> Please use this forum to discuss general LUNG HIV study related topics but not topics specific to a sub-committee. [Feb 13, 2008 1:25:38 PM] Profile PM	Reply to this Post Reply with Quote [Delete this Thread]
ivaleri@ctasc.com Joined: Dec 19, 2007 Posts: 1 Status: Online	Re: Welcome to the Lung HIV Discussion Board! <div style="text-align: center; font-size: 2em; font-weight: bold; color: red;">REPLY</div> Use Post a reply to reply to this post or add a new thread to start a new discussion [Feb 15, 2008 2:17:17 PM] Profile PM	Reply to this Post Reply with Quote [Delete this Post]


[\[Show Printable Version of Thread\]](#) [\[Post new Thread\]](#)




Deleting a thread or post

Only the user that creates the original thread or post may delete it. If you would like to delete a thread or post you created navigate to the thread or post and click on either the *[Delete this Thread]* or *[Delete this Post]* link. This will immediately delete the thread or post and return the user to the Discussion Forum page.



Print a thread

Any user may print all contents of a thread; to do so click on the [Show Printable Version of Thread] link at the bottom of the thread listing or click on the  icon within any post. This will launch a printer-friendly version of the thread and all posts within the thread. Simply use your browser print function to print the thread.

Viewing a user Profile

If you would like to view the Profile of any user you may do so from anywhere within the Forum area where you see a user name listed. In StudyCTMS all usernames are represented by the user's email address. Click on any user's email address or on the  icon within any post and you will be taken to the Profile page for that user.





Sending Private Messages

The Discussion Forum area includes an email capability that allows users to send email to users inside or outside of the system. To send a user a private message either click on the  icon next to any username or within a user post. You may also send a private message by clicking on a user's email address and then clicking on the  icon next to their username on the Profile page.

A private message is created using the same text editor as is used to create a post (pictured above).

Viewing received messages

To view any private messages sent to you click on the *My Private Messages* link on your Profile page. Your private messages will be listed within folders just like within any other email system. Standard folders include Inbox, Draft, Sent and Trash. You can add and edit folders using the *Folder Management* link at the top of your Private Messages page.

Folders	
 Inbox	0
 Draft	0
 Sent	0
 Trash	0
Total: 0	

Viewing Who's online

To see what other users are currently online click the **Who's Online** link in the Discussion Forum menu bar. This will bring the user to a list of all users currently online and what area of the software they are currently utilizing. Click on any user to view their profile.

VISIT

Visit Tab

Visit Forms

StudyCTMS has a complete Electronic Data Capture (EDC) system built in. From the Visit Forms area users may view already-entered forms, edit forms (if they have



sufficient rights), search for forms, export form data for external analysis or enter data into a new form.

When a user arrives at the Visit Forms page he/she will be provided a complete list of all forms that have previously been entered for their site. Only users that have multi-site access will see the Site selection box at the top.

Forms								
Site		Results Per Page		Search				
001		10		<input type="text"/> Advanced Search				
<u>Form ID</u>	<u>Rev</u>	<u>Seq</u>	<u>Subject</u>	<u>Code</u>	<u>Visit#</u>	<u>Visit Date</u>	<u>Status</u>	Clear All Sorts
001	2	0	00101001	JJJ	JJJJ	SEP-25-2007	Keyed - Unchecked	Edit
001	2	0	00101001	JJ	JJJJ	OCT-02-2007	Passing Edit	Edit
001	2	2	00101001	JJJ	JJJJ	OCT-03-2007	Passing Edit	Edit
001	2	0	00102504	RYM	SS01	JUN-01-2007	Passing Re-edit	Edit
001	2	0	00102608	XNE	SS01	JUL-02-2007	Passing Edit	Edit
001	2	0	00102616	EYE	SS01	JUL-03-2007	Passing Edit	Edit
001	2	0	00102358	BZF	SS01	APR-27-2007	Passing Edit	Edit
001	1	0	00101414	GPL	SS01	OCT-31-2006	Passing Edit	Edit
001	1	0	00101172	YZN	SS01	SEP-06-2006	Passing Edit	Edit
001	1	0	00101209	CYJ	SS01	SEP-07-2006	Passing Re-edit	Edit

[Add New Form](#)

1 2 3 4 5 ... [Next](#)

Using the Form list

Many studies are likely to have hundreds to thousands of forms per site. As a result we have provided tools for easily navigating, sorting and searching the Form list.

Any column header that is underlined in the list including Form ID, Subject, Visit#, Visit Date and Status may be clicked on to resort the list. You may select a primary and up to two secondary sorts to find what you are looking for more easily. At any time the user may click the **Clear All Sorts** button to clear all set sorts,

The default setting for this page will show 10 forms per page, however, the user may use the Result Per Page drop down list select a larger number of forms to view per page. At any time the user may also navigate across Form list pages using the pagination controls at the bottom of the list which will include the current page in large print plus a link to go to other pages by number or to the Previous or Next page.

Any user with multi-site access may use the “Site” drop down list to see forms for any other site.

The easiest way to find a form or set of forms that you are looking for is to use the Basic or Advanced Search.

Basic Form Search

The Basic search can be used by simply entering part or all of a subject ID or letter code into the open text box to the right of the word “Search” on the top right of the Form list then hitting the **ENTER** key on your keyboard. This will automatically reload the list with only those forms that fit what was entered into the Search text field.



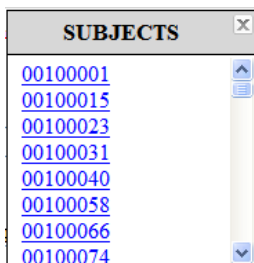
Advanced Form Search

If you desire to find a form or set of form data based on criteria other than just a Subject ID or Letter Code, Advanced Search should be used. To use this feature, click on the *Advanced Search* link immediately under the Search text box.

The Form Search interface includes a blue header bar with the text "Form Search". Below the header, a red instruction reads "Enter as many values as possible, then click Submit." The form is divided into three sections: "SUBJECT" with "Id" and "Code" text boxes; "VISIT" with "Num" and "Date" text boxes and a calendar icon; and "FORM" with "Id", "Rev", and "Seq" text boxes, and an "Edit Status" dropdown menu set to "Select". A red "Submit" button is located at the bottom center.

The Form Search pop-up will now appear offering several additional fields that can be used in a form search. Since the system may contain many subjects and many form IDs, if

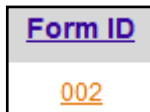
the user clicks into either the Subject ID or Form ID field they will see a pop-up showing all available items. As they enter information into the text field the pop-up box will automatically reduce to only those values that match what has been keyed into the text field. For example, if a user clicks into the Subject ID field they will see a list of all subject IDs pop-up. If they then begin to enter numbers like '0012', the pop-up box will reduce options to only those Subject IDs that begin with '0012'.



To complete your Advanced Search, enter data into as many fields as you desire, then click **Submit**. You will immediately be returned to the Form List page with only those forms showing that meet the criteria you entered. All other Form List features will function as previously discussed.

Viewing a form

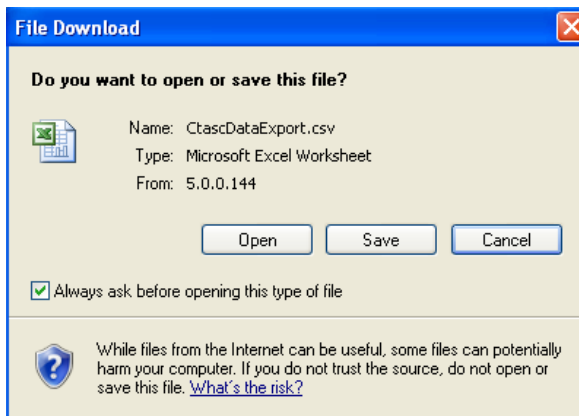
Once you have identified a form you would like to view, simply click on the Form ID to the left of the form you want to view. This will launch the form in view-only mode. The form will be fully functional showing all form tabs, form Q&Q's, field values, errors and error codes but will not have any editable fields or a **Submit** button.



Exporting Form Data

Export Data To export data from StudyCTMS you must have explicit rights to do so provided by a Systems Administrator. To use this feature an Advanced Search must first be conducted. When the results of any Advanced Search are displayed in the Form List a new button will appear at the bottom right of the page to the immediate left of the **Add New Form** button titled **Export data**.

If you wish to export the data for all forms within the Search Results, click on the **Export Data** button. When this button is clicked a new browser window will open up and a Windows download message box will appear offering options of Opening the file in the browser window, Saving the file





to the users local PC or Canceling the request.

If **Open** is selected the file will open in a browser using MS Excel. If **Save** is selected the file will be saved to the user's local hard drive to a location selected by the user. The actual file saved will be in .csv format typically viewed and manipulated using MS Excel.

Click **Cancel** to cancel the request and return to the Form List page.

Adding a new form for data entry

Users must have 'Add' level permissions to any given form in order to enter data for that form. To create a new form for data entry the **Add New Form** button on the bottom of the Form List page must be clicked. When this is done, a list of all forms available to that user appears. Users will only see forms that their user role has 'Add' access to.

Available Forms	
Choose Visit Date First	FEB-15-2008
FORM	Name
001	Subject Screening Form
002	Demographic Questionnaire
003	Change of Procedure Form
010	Medical History Questionnaire
011	Family History Questionnaire
012	Smoking History Form
013	Concomitant Therapy Form
014	Symptom Questionnaire
015	SF-12 Health Survey
016	St. George Respiratory Questionnaire
020	Environmental Questionnaire
021	Occupational and Environmental Questionnaire

To start entering data into a form, the user must first enter the Visit Date in the available field at the top of the Available Forms list. This field will be set to the current days date by default but can be changed by entering a valid date in the correct format or by clicking on the Calendar icon next to the text field. Once the Visit Date is set the user should click the Form ID desired in the

Available Forms list. This will result in a new page titled "Identifying Information".

The header of this page will list the form selected, the Site ID, the Visit Date set on the prior page and the revision number for the form based on the Visit Date selected. The system will automatically identify the revision that was available on the Visit Date set so care should be taken in entering the Visit Date. If an error is made, the *Available*

Available Forms >>>

Identifying Information			
Form: 001	Revision: 2	Site: 001	Visit Date: FEB-15-2008
Enter subject's identifying information, then click Submit.			
Subject:	<input type="text"/>	Letter Code:	<input type="text"/>
Visit:	<input type="text"/>	Seq. #:	<input type="text"/>
<input type="button" value="Submit"/>			

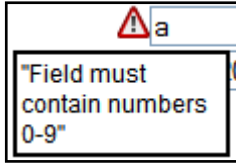
Forms link can be used to return to the prior page. The user must now enter a valid Subject ID, Letter Code (that matches the Subject ID), Visit Number and Sequence # then click **Submit**. If all information is valid the user will be taken to the blank form requested with all subject information automatically passed to that form header.

Every form will vary greatly in its content, therefore specific instructions can not be provided here for each form. Refer to the form Q&Q's included on the last tab of every form for specific directions on completing fields.

There are some common features about form entry that warrant discussion here including range errors, sub-forms and Q&Q's.

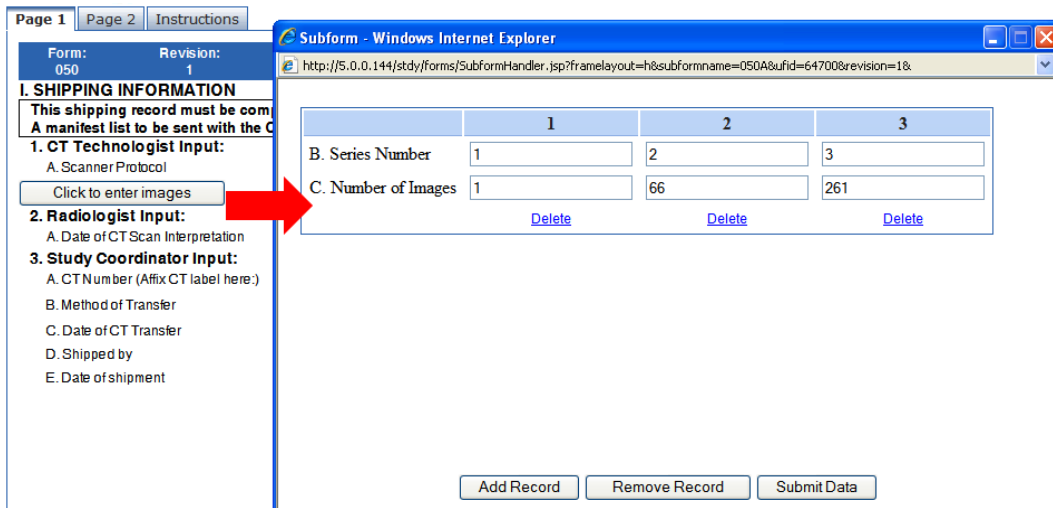
Range Errors

StudyCTMS has a state-of-the-art real time capability to evaluate any field upon data entry to determine whether the value entered violates a data entry range, a human range or a study range. After entering a value in any field and attempting to leave that field, if a range error is detected, an exclamation point graphic will appear. The user may hover over that graphic to receive a detailed message describing the error.



Sub-forms

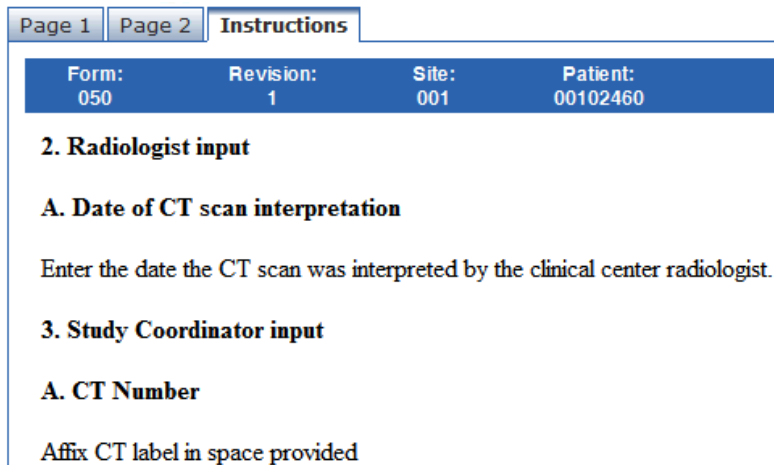
In some cases forms will require one or more sub-forms. A sub-form will appear within the form as a button. When the button is clicked a pop-up will be presented to the user containing all fields in the sub-form. Data can be entered into the sub-form directly and the **Submit Data** button at the bottom used to post the data to the form and the database.



Sub-forms may be presented horizontally (shown) or vertically. A new Column or Row can be added by using the **Add Record** button. A column or row can be deleted by clicking the *Delete* link under a column or to the right of a row. Clicking the **Remove Record** button will delete the last column or row present.

Form Q&Q's

During development of all study forms, a description of how to complete each form section and field is created. To make form completion simple those instructions have been added to each form on a tab titled "Instructions". If instructions are available for a form they will be present as the final tab (far right) on that form.





Users can refer to these instructions as many times as they like during data entry. If the user scrolls down through the instructions then navigates away from the tab then returns their place within the instructions will be maintained.

Editing forms

Users may access forms for edit from the Form List by clicking on the **Edit** button to the right of any form. A detailed description of form editing and validation is discussed in the Form Validation section below.

VALIDATE

Validate Tab

Validate Forms

StudyCTMS has highly complex data testing routines in place to check data entry ranges, human data ranges, study data ranges and multi-field and multi-form data consistency.

As a result many forms, upon initial submission, will contain one or more errors. As data edits and validation are a critical part of ensuring data quality, StudyCTMS provides specific tools to assist in validating errors. The validate forms feature provides a list of all forms with errors including a count of the error present. The Validate Forms list contains all of the features of the Forms List with the

Validate Forms									
Site		Results Per Page		Search					
001		10		Advanced Search					
Form ID	Rev	Seq	Subject	Code	Visit#	Visit Date	Status	# Errors	Clear All Sorts
002	0	0	00101345	EPQ	DQ01	OCT-19-2006	Failing Edit	1	Edit
002	0	0	00101740	NKU	DQ01	JAN-08-2007	Failing Edit	3	Edit
002	0	0	00102521	ZQB	DQ01	JUN-06-2007	Failing Edit	1	Edit
010	0	0	00100650	FGL	MH01	JAN-20-2006	Failing Edit	2	Edit
010	0	0	00102169	CFP	MH01	MAR-19-2007	Failing Edit	2	Edit
010	0	0	00102547	GKY	MH01	JUN-07-2007	Failing Edit	3	Edit
012	0	0	00101774	EJK	SH01	JAN-09-2007	Failing Edit	1	Edit
032	1	0	00100737	YJR	PF01	MAR-07-2006	Failing Edit	3	Edit
040	2	0	00102151	XLP	LD01	MAR-19-2007	Failing Edit	6	Edit
062	1	0	00100031	YOK	CD01	MAR-27-2006	Passing Edit	1	Edit

exception of the absence of the **Add New Form** button. From the Validate Forms page users can sort, search and view forms in the exact same manner as described in the Form List section above except that ALL results shown will only include forms that contain at least one non-validated error.

The Error column shows a count of all forms errors that have NOT been validated or corrected to date. To enter a form to edit, the user clicks on the **Edit** button to the right of the form they desire to edit.

When the form appears all errors will be shown with one of two types of icons.


Page 1 | Page 2 | Instructions

Form: 040 Revision: 1 Site: 001 Subject: 00100031 Letter Code: Visit: LD01 Seq. #: 0 Visit Date: MAR-18-2005


I. Blood Tests

Complete Question 1 for all patients.

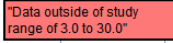
1. CBC

A. Date of CBC MAR-23-2005  Not Done

If CBC not done go to question 2.

B. WBC  59.3 Not Done

C. WBC Differential

1. neutrophils(%)  "Data outside of study range of 3.0 to 30.0"

2. lymphocytes(%) 23.26

3. monocytes(%) 9.94

4. eosinophils(%) 2.63

5. basophils(%) .94


D. Hgb (g/dL) 13.7 Not Done

E. Hematocrit(%) 39.6 Not Done


F. Platelets (X 10**9/L) 170 Not Done


2. Lab Chemistries


Complete Question 2 if a patient has a clinical indication of IPF.


A. Date of Lab Chemistries  Not done

If Not Done go to Question 3.


B. Rheumatoid Factor (RF) Present Absent Not Done Clear Item 

C. Creatine Kinase (CK) (U/L)  Not done

D. Erythrocyte Sedimentation Rate (ESR) (mm/hr)  Not done

All range errors (data entry, human and study) are shown using an exclamation point icon . If the user hovers over this icon they will be presented with a description of the range error including the valid range.

"Data outside of study range of 3.0 to 30.0"

All consistency errors appear as a colored square with a number. The number indicates the consistency error group and the color is present to make visual connection between related fields in error easier to identify. For example, a consistency check with  next to it indicates that this field and any other fields with that same icon present are part of a consistency question error. Any one form may have any number of consistency errors impacting any number of fields. One field on any form can also be part of any number of consistency errors and may, therefore, have multiple square, numbered icons next to it.

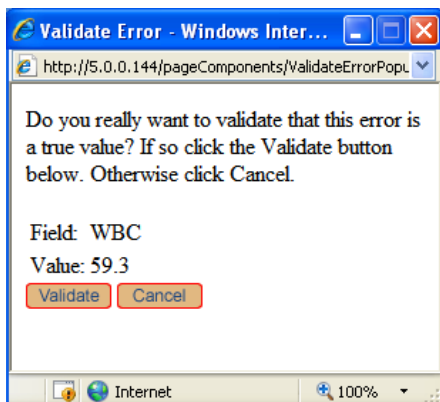
"If CBC not done, date should not be specified. Otherwise date should be answered"

Hovering over a consistency error will also cause the appearance of a message box describing the error


Validating errors

The user may choose to enter any field in error at any time to correct it. In the case of range errors, users may validate the error.

In some cases even though a human or study range has been validated, the site may wish to validate that the value entered into the field is valid. When this occurs the user should navigate to the field in question and double-click on the exclamation point icon. Data entry range errors may not be validated as they indicate values that are not possible for database storage in that field. For example, attempted entry of the letter 'k' into a number field.





If, when presented with the Validate Error pop-up, the user clicks the **Validate** button, the pop-up will close, the data point will be stored as “validated” in the database and the exclamation point icon will change from red to yellow . At any time, if a user decides that the field was validated in error, they simply need to double-click on the yellow icon and choose “Yes” when asked if they want to undo the validation.

ANALYZE

Analyze Tab

Standard Models

<section to be added in next version of this document>

**LONGITUDINAL STUDIES OF HIV-ASSOCIATED
LUNG INFECTIONS AND COMPLICATIONS
(LUNG HIV)
MANUAL OF OPERATIONS**

Appendix C

List of Common Study Forms

Form 001	Contact Form
Form 002	Demographics Form
Form 003	Pulmonary HIV Questionnaire
Form 004	Pulmonary HIV Diagnosis Form
Form 005	Laboratory Abstraction Form (only at sites collecting specimens)
Form 006	Pulmonary Function Testing Form
Form 007	CT Scan Report (only at sites performing CT scans)
Form 008	BAL Form
Form 009	Missed Visit Form
Form 010	Deactivation Form
Form 011	Death Form
Form 012	Serious Adverse Event Form

**LONGITUDINAL STUDIES OF HIV-ASSOCIATED
LUNG INFECTIONS AND COMPLICATIONS
(LUNG HIV)
MANUAL OF OPERATIONS**

Appendix D

Schedule of Procedures

This section is currently under development.
Varies according to site.

**LONGITUDINAL STUDIES OF HIV-ASSOCIATED
LUNG INFECTIONS AND COMPLICATIONS
(LUNG HIV)
MANUAL OF OPERATIONS**

Appendix E

Informed Consent Templates

Revised 5/2011

INFORMED CONSENT TEMPLATE

INFORMED CONSENT TO PARTICIPATE IN THE LUNG HIV RESEARCH STUDY

1. INTRODUCTION

In addition to Dr. _____'s research on pulmonary HIV infection entitled _____. He/she is participating in a NHLBI-funded study entitled the Longitudinal Studies of HIV-Associated Lung Diseases and Complications (Lung HIV) which is designed to study the pulmonary complications that can occur in individuals infected with the HIV-1 virus. In addition to a specific Lung HIV study being conducted at <HOSPITAL>, Dr. _____ has agreed to provide outcome data, treatment data, the results of procedures and tests, and questionnaire data in a standard format so that research can be carried out using information from all of the participating hospitals.

2. PURPOSE OF THIS RESEARCH STUDY

The purpose of the Lung HIV study is to collect standardized information and blood specimens from seven different hospitals over a five-year period to help the Lung HIV investigators to understand the lung-related complications of HIV infection and how these complications may be treated better.

3. LENGTH OF YOUR PARTICIPATION

Your participation in the study will last until <END DATE>. Dr. _____ and his/her staff will collect information for the Lung HIV study every six months until <END DATE>. In most instances, your visit for this study will be combined with the visit for <INSERT NAME OF SPECIFIC LUNG HIV STUDY AT THE HOSPITAL>. We will collect a blood sample from you every six months until the end of the study.

4. WHERE THE STUDY IS BEING DONE AND NUMBER OF PEOPLE PARTICIPATING

There are seven other nationally recognized hospitals that will be participating in this study. There is a coordinating center located in Baltimore Maryland which will be responsible for storing the data. Individuals at the NHLBI will also have access to these data. About _____ patients total will take part in the common part of the Lung HIV study, the <HOSPITAL> will be responsible for providing _____ of these patients.

5. STUDY PROCEDURES

Before you take part in this research study, the study must be explained to you and you must be given the chance to ask questions. You must read and sign this informed consent form. You will be given a copy of this consent form to take home with you.

If you agree to take part in this study, the following will happen every six months

- **Questionnaires** – you will be asked to answer questions about your symptoms, the history of your lung disease, lung irritants you may have been exposed to in the past and

a series of questions and measurements to assess the activity of your lung disease. This will take approximately one hour.

- **Lung function testing** – *Spirometry* consists of breathing tests that measure the amount of air your lungs can blow out. During the test, you will be asked to blow forcefully into a mouthpiece, while a machine measures the amount of air you are breathing. *Plethysmography and Diffusing Capacity for Carbon Monoxide (DLCO)* – you will be asked to sit in a clear, airtight box called a plethysmograph to undergo certain other breathing tests. These lung functions tests will take approximately 1 hour.
- **Blood tests** – Approximately 4 tablespoons of blood will be drawn from a vein in your arm. Some of the blood will be used for routine clinical laboratory tests. About 2 tablespoons of this blood will be sent to and stored at a central blood bank for future studies.

Results obtained from the blood tests, including CBC and various rheumatologic serologies will be provided to both the site Principal Investigator as well as your primary physician. Please check the box below if you wish to obtain a copy of these results.

I would like to have a copy of my blood test results. _____ Initials

I give permission for my blood products to be stored at a central blood bank:

- Only for the Lung HIV Study
- For any HIV-related Study
- For any study _____ Initials

- **CT scan of your lungs** – to take the CT scan of your lungs, several sets of x-ray pictures will be taken. This test will take approximately 1 hour. Each set of pictures will require you to hold your breath either in or out as best you can for up to 15 seconds. Some images may be taken with you lying on your stomach. These pictures include:
 - Images used to find your lungs and plan the CT scan
 - Images taken with you holding your breath in
 - Images taken with you holding your breath out
 - Images taken with you lying on your stomach

If we are not able to take a CT scans as just described, we will ask for a copy of a CT scan you may have had in the last six months. We will use this copy of the previously taken CT scan for our research.

The CT scan will be examined by a hospital radiologist (a doctor who reads x-rays). A report will go in your medical record.

A copy of your CT scan will be kept by researchers at the <Clinical Center> for examination by a research radiologist and permanent storage. All information that would identify you will be removed from these research copies and replaced with a code for identification. The copy of the CT scan will become the property of the study and may be used for future research. If a copy of your CT scan is requested by outside researchers, the study code will be destroyed and there will be no way to retrieve this CT as it has been made completely anonymous.

You can still be part of the study even if you cannot complete a CT scan of your lungs and an earlier CT scan is not available.

- **Medical Records Review** - Information from your medical record may allow researchers to better understand what causes lung diseases such as yours. Study researchers will look at your medical records so they can learn important information about your medical history that may be related to your lung problem.

6. WHAT WILL HAPPEN WHEN YOU COMPLETE THE STUDY

As the investigators learn more about the pulmonary complications of HIV, they will publish papers in peer-reviewed journals. These papers will be present on the Lung HIV public Web page (lungshiv.com) and you will be free to review these papers. When the study ends, you will be contacted by mail with a brief summary of the study's findings. At the conclusion of the study, all study numbers related to you will be removed from your data and the information collected will be provided to the NHLBI for public research. Once this is done, there will be no way for an investigator requesting these data to know your identity.

7. PROCEDURES THAT ARE NOT STANDARD CARE FOR YOUR CONDITION OR ARE EXPERIMENTAL.

All procedures used in this study are part of the regular treatment of patients with lung complications of HIV.

8. POSSIBLE RISKS OR SIDE EFFECTS OF TAKING PART IN THIS STUDY.

Taking blood from a vein may cause some discomfort and occasionally cause some bleeding or bruising at the site. This could cause you to faint.

During the lung function tests you may have difficulty breathing and you may become fatigued, but you will be allowed to rest periodically. You may become short of breath while doing the breathing tests. In rare cases, people may experience syncope (brief loss of consciousness) and fainting during spirometry procedure. You may be given medicine to help your breathing improve if this occurs.

There are possible expected and unexpected risks of the CT scan. These include the discovery of unexpected findings (for example cancerous tumors or an infection) which you may not know about now, which could cause you to require more tests.

The CT scan will involve the delivery of small amounts of radiation to your body. The amount of radiation you will receive has a low risk of harmful effects. Your radiation exposure is generally considered to be less than one tenth of one percent (0.1%) of your lifetime risk of developing a fatal cancerous tumor as a result of this radiation.

If a previously obtained CT scan is used, there will be no additional and unexpected risks in connection with the CT scan.

Other risks associated with the exercise test are:

- Accidental injury
- Discomfort during the test

- Coughing or shortness of breath
- You may get tired and light-headed

On rare occasions, exercise can lead to collapse or to a heart attack.

While you are taking part in this study, you are at risk for these potential side effects. You should talk to the researcher and/or your medical doctor about these side effects if you have questions or concerns. There also may be other side effects that are not known. The LTRC investigators will monitor you for 24 hours after the lung function tests and the CT scan to ascertain the safety of these procedures.

9. IMPORTANT INFORMATION FOR WOMEN

There is not enough medical information to know what the risks might be to a breast-fed infant or an unborn child carried by a woman who takes part in this study. Therefore, women who can become pregnant must have a negative pregnancy test before taking part in this study. For the pregnancy test, you will give a blood sample taken from a vein in your arm by a needle 2 days before the CT scan. You will be told the results of the pregnancy test. If the pregnancy test is positive, you will not be able to have the CT scan but can participate in the other aspects of the study.

10. COSTS FOR TAKING PART IN THIS STUDY

Any study-related procedure such as: _____ will be free to you during the study. You or your insurance company will have to pay for your normal care related to pulmonary complications of HIV.

11. PAYMENT FOR TAKING PART IN THIS STUDY

You will be paid as follows: If you complete the study, you will be paid _____. If you do not complete the study for any reason, you will be paid _____ for each visit you complete.

12. POSSIBLE BENEFITS TO YOU FOR TAKING PART IN THE STUDY

There are no direct benefits to you for participating in this study. However, your participation in this study may add to the medical knowledge about these conditions.

13. OTHER TREATMENTS AVAILABLE

This study has no required medical treatments. All treatments will be guided by your treating physician.

14. ABOUT PARTICIPATING IN THIS STUDY

Your participation in this study is voluntary. You may stop participating in this study at any time. Your decision not to take part in this study or to discontinue participation will not affect your medical care or any benefits to which you are entitled. If you decide to stop taking part in this study, you should tell the investigator.

Your doctor and the investigator may stop your participation in the study at any time if they decide that it is in your best interest. They may also do this if you do not follow instructions. If you have other medical problems or side effects, the doctor and/or nurse will decide if you may continue in the research study.

15. COMPENSATION FOR INJURY

By signing this consent form, you will not waive any of your legal rights or release the parties involved in this study from liability for negligence.

16. CONFIDENTIALITY OF STUDY RECORDS AND MEDICAL RECORDS

Information collected for this study is confidential. However, the NHLBI, and the coordinating center will receive copies of the study records. Employees of the NHLBI, and C-TASC (the coordinating center), and the Institutional Review Board (IRB) may see parts of your medical records related to this study. Data collected and entered into the Case Report Forms and specimens collected and stored at the central blood bank are the property of the NHLBI. In the event of any publication regarding the study, your identity will not be disclosed.

17. RELEASE OF PERSONAL INFORMATION

Some of the questions asked and the information collected may be private and confidential. We will not identify you in any way other than to assign a patient number for the collection of your data.

To help us protect your privacy, we will apply for a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

At the end of the study, all identifying information that could possible link the data and specimens to you will be deleted and will no longer be available to researchers outside of the Lung HIV study.

18. NAMES OF CONTACTS FOR QUESTIONS ABOUT THE STUDY

If you have any questions about taking part in this study, or if you think you may have been injured because of the study, call _____ at _____. If you have

any questions about your rights as a research subject, you can call the Institution Review Board at _____.

VOLUNTEER'S STATEMENT

I have been given a chance to ask questions about this research study. These questions have been answered to my satisfaction. If I have any more questions about taking part in this study or research-related injury, I am to contact _____ at _____.

I understand that my participation in this research project is voluntary. I know that I may quit the study at any time without harming my future medical care or losing any benefits to which I may be otherwise entitled. I also understand that the investigator in charge of this study may decide at any time that I should no longer participate in this study.

If I have any questions about my rights as a research subject in this study I may contact:

IRB Chairperson Name
Address
Telephone (Collect calls will be accepted)

By signing this consent form, I have not waived any of my legal rights or released the parties involved in this study from liability for negligence.

I have read and understand the above information. I agree to participate in this study. I have been given a copy of this form for my own records.

_____	_____
Study Participant (Signature)	Date
_____	_____
Print Participant's Name	Date
_____	_____
Signature of Person who Explained the Study	Date
_____	_____
Principal Investigator	Date

**LUNG HIV
INFORMED CONSENT TEMPLATE**

INFORMED CONSENT TO PARTICIPATE IN THE LUNG HIV RESEARCH STUDY

1. INTRODUCTION

In addition to Dr. _____'s research on pulmonary HIV infection entitled _____, He/she is participating in a NHLBI-funded study entitled the Longitudinal Studies of HIV-Associated Lung Diseases and Complications (Lung-HIV) which is designed to study the pulmonary complications that can occur in individuals infected with the HIV-1 virus. In addition to a specific Lung HIV study being conducted at <HOSPITAL>, Dr. _____ has agreed to collect blood and bronchoalveolar lavage (BAL) samples and provide them to a central repository, provide outcome data, treatment data, the results of procedures and tests, and questionnaire data in a standard format so that research can be carried out using information from all of the participating institutions.

2. PURPOSE OF THIS RESEARCH STUDY

The purpose of the Lung HIV study is to collect standardized information and laboratory specimens (blood and BAL) from seven different institutions over a five-year period to help the Lung HIV investigators better understand the lung-related complications of HIV infection and how these complications may be treated more effectively and efficiently.

3. LENGTH OF YOUR PARTICIPATION

Your participation in the study will last until <END DATE>. Dr. _____ and his/her staff will collect information for the Lung HIV study every six months until <END DATE>. In most instances, your visit for this study will be combined with the visit for <INSERT NAME OF SPECIFIC LUNG HIV STUDY AT THE HOSPITAL>. We will collect blood from you every six months until the end of the study. BAL samples will be collected when, as part of a procedure for another study or as part of Dr. _____'s protocol, a BAL procedure is performed.

4. WHERE THE STUDY IS BEING DONE AND NUMBER OF PEOPLE PARTICIPATING

There are seven other nationally recognized institutions that will be participating in this study. There is a coordinating center located in Baltimore, Maryland which will be responsible for storing the clinical data connected to your blood and BAL samples. Individuals at the NHLBI will also have access to these data. About _____ patients total will take part in the common part of the Lung HIV study, the <HOSPITAL> will be responsible for providing _____ of these patients.

5. STUDY PROCEDURES

Before you take part in this research study, the study must be explained to you and you must be given the chance to ask questions. You must read and sign this informed consent form. You will be given a copy of this consent form to take home with you.

If you agree to take part in this study, the following will happen every six months

- **Blood tests** – Approximately 4 tablespoons of blood will be drawn from a vein in your arm. Some of the blood will be used for routine clinical laboratory tests. About 2 tablespoons of this blood will be sent to and stored at a central blood bank for future studies.

If BAL fluid is collected as part of other Lung HIV studies, approximately _____ tablespoons of this fluid will be sent to the specimen bank.

Results obtained from the blood tests, including CBC and various rheumatologic serologies will be provided to both the site Principal Investigator as well as your primary physician. Please check the box below if you wish to obtain a copy of these results.

I would like to have a copy of my blood test results. _____ Initials

I give permission for my blood products and BAL to be stored at a central specimen bank:

- Only for a Lung HIV Study
- For any HIV-related Study
- For any study _____ Initials

Genetic studies may also prove valuable in helping investigators understand HIV and pulmonary disease.

I give permission for my genetic studies to be performed on blood products and BAL:

- Only for a Lung HIV Study
- For any HIV-related Study
- For any study _____ Initials

- **Medical Records Review** - Information from your medical record may allow researchers to better understand what causes lung diseases such as yours. Study researchers will look at your medical records so they can learn important information about your medical history that may be related to your lung problem.

6. WHAT WILL HAPPEN WHEN YOU COMPLETE THE STUDY

As the investigators learn more about the pulmonary complications of HIV, they will publish papers in peer-reviewed journals. These papers will be present on the Lung HIV public Web page (www.lunghiv.com) and you will be free to review these papers. When the study ends, you will be contacted by mail with a brief summary of the study's findings. At the conclusion of the study, all study numbers related to you will be removed from your data and the information collected will be provided to the NHLBI for public research. Once this is done, there will be no way for an investigator requesting these data to know your identity.

7. PROCEDURES THAT ARE NOT STANDARD CARE FOR YOUR CONDITION OR ARE EXPERIMENTAL.

All procedures used in this study are part of the regular treatment of patients with lung complications of HIV.

8. POSSIBLE RISKS OR SIDE EFFECTS OF TAKING PART IN THIS STUDY.

Taking blood from a vein may cause some discomfort and occasionally cause some bleeding or bruising at the site. This could cause you to faint.

9. COSTS FOR TAKING PART IN THIS STUDY

The blood draw will be free to you during the study. You or your insurance company will have to pay for your normal care related to pulmonary complications of HIV.

10. PAYMENT FOR TAKING PART IN THIS STUDY

You will be paid as follows: If you complete the study, you will be paid _____. If you do not complete the study for any reason, you will be paid _____ for each visit you complete.

11. POSSIBLE BENEFITS TO YOU FOR TAKING PART IN THE STUDY

There are no direct benefits to you for participating in this study. However, your participation in this study may add to the medical knowledge about these conditions.

12. OTHER TREATMENTS AVAILABLE

This study has no required medical treatments. All treatments will be guided by your treating physician.

13. ABOUT PARTICIPATING IN THIS STUDY

Your participation in this study is voluntary. You may stop participating in this study at any time. Your decision not to take part in this study or to discontinue participation will not affect your medical care or any benefits to which you are entitled. If you decide to stop taking part in this study, you should tell the investigator.

Your doctor and the investigator may stop your participation in the study at any time if they decide that it is in your best interest. They may also do this if you do not follow instructions. If you have other medical problems or side effects, the doctor and/or nurse will decide if you may continue in the research study.

14. COMPENSATION FOR INJURY

By signing this consent form, you will not waive any of your legal rights or release the parties involved in this study from liability for negligence.

15. CONFIDENTIALITY OF STUDY RECORDS AND MEDICAL RECORDS

Information collected for this study is confidential. However, the NHLBI, and the coordinating center will receive copies of the study records. Employees of the NHLBI, and C-TASC (the coordinating center), and the Institutional Review Board (IRB) may see parts

of your medical records related to this study. Data collected and entered into the Case Report Forms and specimens collected and stored at the central blood bank are the property of the NHLBI. In the event of any publication regarding the study, your identity will not be disclosed.

16. RELEASE OF PERSONAL INFORMATION

Some of the questions asked and the information collected may be private and confidential. We will not identify you in any way other than to assign a patient number for the collection of your data.

To help us protect your privacy, we will apply for a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally-funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

At the end of the study, all identifying information that could possibly link the data and specimens to you will be deleted and will no longer be available to researchers outside of the Lung HIV study.

17. NAMES OF CONTACTS FOR QUESTIONS ABOUT THE STUDY

If you have any questions about taking part in this study, or if you think you may have been injured because of the study, call _____ at _____. If you have any questions about your rights as a research subject, you can call the Institution Review Board at _____.

VOLUNTEER'S STATEMENT

I have been given a chance to ask questions about this research study. These questions have been answered to my satisfaction. If I have any more questions about taking part in this study or research-related injury, I am to contact _____ at _____.

I understand that my participation in this research project is voluntary. I know that I may quit the study at any time without harming my future medical care or losing any benefits to which I may be otherwise entitled. I also understand that the investigator in charge of this study may decide at any time that I should no longer participate in this study.

If I have any questions about my rights as a research subject in this study I may contact:

IRB Chairperson Name
Address
Telephone (Collect calls will be accepted)

By signing this consent form, I have not waived any of my legal rights or released the parties involved in this study from liability for negligence.

I have read and understand the above information. I agree to participate in this study. I have been given a copy of this form for my own records.

Study Participant (Signature)

Date

Print Participant's Name

Date

Signature of Person who Explained the Study

Date

Principal Investigator

Date

**LONGITUDINAL STUDIES OF HIV-ASSOCIATED
LUNG INFECTIONS AND COMPLICATIONS
(LUNG HIV)
MANUAL OF OPERATIONS**

Appendix F

Repository Concept Sheet

Concept for the handling of whole blood and BAL samples collected for the Lung HIV Repository at BBI SeraCare

Specimens for the Lung HIV Study are to be collected in addition to those used for clinical assessment and treatment. They are to be stored in a central repository for the use of future studies. This concept is not intended to guide or interfere with the handling of samples collected for clinical assessment or medical treatment. *All reference to 'specimens' in this concept is to NHLBI Lung HIV repository-directed specimens only.* This concept is not intended to replace any specimen handling systems, but to work in conjunction with existing systems, and uses both 2-dimensional (2D) and 1-dimensional (1D) bar codes to provide both a repository and Lung HIV Study specimen identification number. Management of all phases of collection, processing, and shipment can be done online through StudyCTMS (www.studyctms.com).

Collection

After a subject has consented to have tissues in the Lung HIV repository, sample collection will occur as designated by the Clinical Site. While the specifics of collection (collection location, amount, and tissue type) may vary according to site-specific protocol, the investigators have agreed to collect specimens as outlined in Chapter 5 of the Lung HIV Common Study Manual of Operations (online at www.studyctms.com).

When a subject is due for a clinic visit where a blood specimen for the repository is to be drawn, Clinical Site staff should assemble the following:

Forms

Blank study forms can be printed from StudyCTMS.

- Repository Registration Form - to document consent and enter the subject into the electronic repository system (This form is completed only one time per subject contributing samples to the repository. It must be submitted in StudyCTMS before any specimen collection data can be entered.)
- Specimen Form - to document assignment of a Specimen Label Set identifier to a specific Lung HIV subject and sample being collected

Specimen Label Set (one set of labels per specimen)

Specimen Label Sets will be distributed by C-TASC for use at sample collection. One Label Set is to be used for each specimen type (whole blood or BAL). Each Label Set is assigned a unique number that 'owns' any additional identification numbers within it. Each Specimen Label Set contains the following:

1D labels for Specimen Form and collection vessel

Two identical 1D bar code labels display a specimen ID that links data in StudyCTMS to the BSI Numbers (repository IDs) used for the aliquot tubes. For Clinical Sites using intermediary labs/repositories, these labels may instead contain information specific to these repositories to ensure cohesive transition. (*This information must be provided to C-TASC before*

any sample collection to ensure proper specimen identification within StudyCTMS.)

2D labels for Specimen Form each aliquot tube

BBI SeraCare has assigned the Lung HIV Study a block of unique numbers for use in labeling aliquot vials to be stored in the repository. These labels display a 2D bar code, an alphanumeric representation of the BSI Number, and text describing the sample type (i.e., 'PLASMA', or 'BAL SUP') to be stored in the vial. No subject-specific information can be determined from the information printed on these labels. (See example below.)

Once the biological specimen has been obtained, the collection vessel is immediately labeled with one of the 1D labels. (For site-specific protocols where banked specimens are used, this 1D label is simply affixed to the vial containing the sample.) The matching ID label is then affixed to the Specimen Form, thus linking the specimen to the subject. The information on the Specimen Form should be entered into StudyCTMS at the Clinic Site immediately after sample collection.

Processing

There is great procedural variability among the Lung HIV Clinical Sites regarding their sample processing arrangements. It is the intent of this concept not to interfere with these processes and place minimal burden on Clinical Site and laboratory staff.

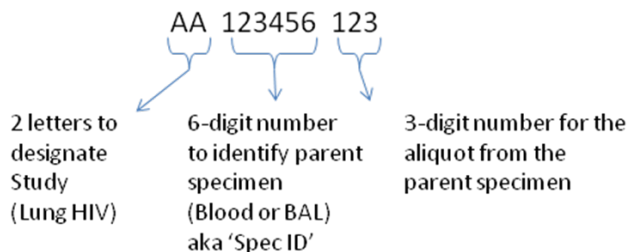
The individual processing the sample should put final aliquots into designated cryovials, label any tubes that contain final aliquots with 2D labels, and log all final aliquots into StudyCTMS. Samples going to an additional repository or lab prior to shipment to BBI SeraCare can be tracked using identification variables supplied to C-TASC from these additional repositories (given that these codes are supplied to C-TASC *prior to the advent* of specimen collection).

Storage until shipment

StudyCTMS will contain information on all samples collected, the aliquots they yield, and the extent of patient consent. Investigators can easily inventory all available samples online - not just their own. StudyCTMS will also be used to develop manifests needed for shipment to the repository and/or from the repository to an investigator using Lung HIV samples for additional research.

Anatomy of a repository specimen identification number (BSI)

The BSI Numbers designated by BBI SeraCare for NHLBI specimens have the following structure:



Anatomy of a 1D label for Lung HIV

The following is an example of the 1D bar code label. 1D labels contain the specimen ID which has been provided to C-TASC by external sources (BBI SeraCar, Maverick, etc.).



Anatomy of a 2D label for Lung HIV repository aliquots

The following is an example of the label supplied by BBI SeraCare to the Clinic Sites (enlarged to show detail).



Outline for one tube of whole blood

It is understood that at pre-determined times, an additional purple-top vacutainer of whole blood will be collected at some Clinical Sites for the purpose of contributing samples (plasma and packed cells) to the repository.

Outline for one BAL specimen

It is understood that BALs will be performed by only select Clinical Sites. Further, BALs will not be performed simply to collect specimens for the Lung HIV repository and only such materials that remain after a clinically relevant BAL is performed will be contributed. It is also understood that there may not be enough cells suspended in any remaining BAL fluid to constitute a cell pellet, and that pellets will only be contributed to the repository where possible given this constraint.

Advantages of this concept

1. No subject information on the sample tubes
2. Accommodates NHLBI or external repository specimen IDs
3. Minimal burden on laboratory staff
4. Rugged data linkages at critical points (labeling and scanning)

Samples already being collected from enrolling Clinical Sites

The NHLBI Lung HIV specimen repository is currently undergoing the application process. As a condition of their Lung HIV award, investigators at enrolling Clinical Sites may already be collecting specimens for this repository. Until the repository is realized and submission processes are finalized, investigators will store any specimens locally.

BAL specimens

BAL fluid that is designated for the repository should be processed according to the Common Lung HIV BAL Processing Protocol.

Blood specimens

Whole blood specimens should be processed according to the Common Lung HIV Specimen Processing Protocol.

**LONGITUDINAL STUDIES OF HIV-ASSOCIATED
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Appendix G

Specimen Collection Plan

**LONGITUDINAL STUDIES OF HIV-ASSOCIATED
LUNG INFECTIONS AND COMPLICATIONS
(LUNG HIV)
MANUAL OF OPERATIONS**

Appendix H

Repository Sample Collection and Processing Protocol (Blood)

Lung HIV Repository Sample Collection and Processing Protocol

1. PURPOSE

To outline the responsibilities and to define the steps to be followed for separation of plasma and packed cells from whole blood to ensure consistency.

2. SCOPE

This procedure is used for specimens that require plasma and packed cells isolation by centrifugation.

Packed cells is defined as all remaining material after the plasma has been separated via centrifugation from the whole blood. This includes buffy coat, red blood cells, and granulocytes.

3. MATERIALS REQUIRED

- Sterile Polypropylene Centrifuge Tubes
- Sterile Serological Pipettes
- 2 ml Sarstedt Cryovials (or equivalent 2 ml cryovials with skirt and o-ring)
Source: <http://scimart.com/screwcapmicrotubeskirt2ml1000case.aspx>
- Freezer storage boxes (5 1/4" x 5 1/4" x 2.2" , 9x9 grid, polycarbonate, or equivalent)
Source: <http://www.evergreensci.com/cs/csba.htm>
- Study Forms (print from Study CTMS)

4. EQUIPMENT REQUIRED

- Centrifuge capable of 900 x g
- Biohazard Safety Hood

5. PROCEDURE

Note: Blood should be processed within 6 hours of collection and must be stored at refrigerated temperatures (2°C to 8°C).

Pre-Processing Steps:

1. Label all cryovials needed with the provided BSI ID Barcode labels
(Accession # unique to the draw of a participant followed by unique vial number).
The cryovials are labeled for the final product, e.g., plasma.
2. Record required data associated with the sample as you prepare and process the whole blood. This is documented on the Specimen Form.
3. Verify that the labeling is correct.

4. Verify all identifiers before each transfer step is begun. You are verifying that prior to transferring blood from one vessel to another that the ID's are the same on each tube, so as not to combine two patients.

Processing of Whole Blood

Transfer the fresh blood samples in a biosafety hood for processing. Place the tubes from one individual patient sample ID into a rack. Never put tubes from two different samples into the same rack to prevent accidental mixing of patient samples.

1. Centrifuge the tubes at 900-1200 x g for 20 minutes at room temperature.
2. Using a sterile pipette, remove the plasma, and aliquot plasma into the appropriate pre-labeled cryovials at the designated volume (Leave approximately 2 ml on top of the cell layer). Aliquot as follows:

2ml Cryovials
4 vials at 0.75 ml

3. Mix the remaining whole blood (Packed Cells) by aspirating and dispensing at least 60% of the volume three times and immediately aliquot as follows:

2ml Cryovials
4 vials at 0.50 ml

4. Place cryovials in freezer storage boxes.
5. Document the # of cryovials and volumes by material type on the Specimen Form and store the plasma and packed cell vials between -70 and -80°C. Document the location for later retrieval purposes.

**LONGITUDINAL STUDIES OF HIV-ASSOCIATED
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Appendix I

**Repository Sample Collection and Processing Protocol
(BAL)**

The BAL Processing SOP's are site-specific