

CONFIDENTIAL



Manual of Operating Procedures

CleanUP-IPF Trial

STUDY OF CLINICAL EFFICACY OF ANTIMICROBIAL THERAPY
STRATEGY USING PRAGMATIC DESIGN IN IDIOPATHIC PULMONARY
FIBROSIS (CLEANUP-IPF)

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1.0 CleanUP-IPF-IPF TRIAL OVERVIEW

Title:	Study of <u>C</u>linical <u>E</u>fficacy of <u>A</u>ntimicrobial Therapy Strategy Using <u>P</u>ragmatic Design in <u>I</u>diopathic <u>P</u>ulmonary <u>F</u>ibrosis (CleanUP-IPF)
Location:	Approximately 20-40 clinical sites in the United States
Objectives:	To compare the impact of an antimicrobial therapy strategy on clinical outcomes
Study Design:	500-patient, randomized, un-blinded, phase III, multicenter clinical trial of an antimicrobial therapy strategy in idiopathic pulmonary fibrosis patients
Treatment Regimens:	1:1 randomization to either oral antibiotic (co-trimoxazole or doxycycline) in addition to standard-of-care or standard-of-care alone. The subject randomized to antimicrobial therapy will be treated with trimethoprim 160mg/800mg sulfamethoxazole (double strength co-trimoxazole) twice a day plus folic acid 5 mg daily unless there is a contraindication to this therapy. If the subject develops an intolerance to co-trimoxazole the dosage can be decreased to once a day 160mg trimethoprim/800mg sulfamethoxazole (one double strength co-trimoxazole) three times weekly plus folic acid 5 mg daily. If intolerance continues with co-trimoxazole then the antimicrobial agent can be changed to doxycycline (without folic acid). Subjects with a contraindication to co-trimoxazole will be treated with doxycycline (without folic acid). Doxycycline will be dosed at 100 mg once daily if body weight is < 50 kg and 100 mg twice daily if $\geq$ 50 kg.
Primary Endpoint:	Time to first non-elective respiratory hospitalization or all-cause mortality
Secondary Endpoints:	• Time to death from any cause • Time to first non-elective, respiratory hospitalization • Time to first non-elective, all-cause hospitalization • Total number of non-elective respiratory hospitalizations • Total number of non-elective all-cause hospitalizations • Change in FVC from randomization to 12 months • Change in DLCO from randomization to 12 months

	• Total respiratory infections • Change in UCSD-Shortness of Breath Questionnaire and Fatigue Severity Scale score from randomization to 12 months • Change in Leicester Cough Questionnaire score from randomization to 12 months • Change in EQ-5D score and SF-12 score from randomization to 12 months • Change in ICEpop CAPability measure for Older people (ICECAP-O) score from randomization to 12 months
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2.0 OBJECTIVES OF THE MANUAL OF OPERATING PROCEDURES

The purpose of the CleanUP-IPF Manual of Operating Procedures (MOP) is to provide detailed instruction in the performance of research procedures associated with the study.

This MOP serves as a reference for study staff to enhance consistency among the clinical centers.

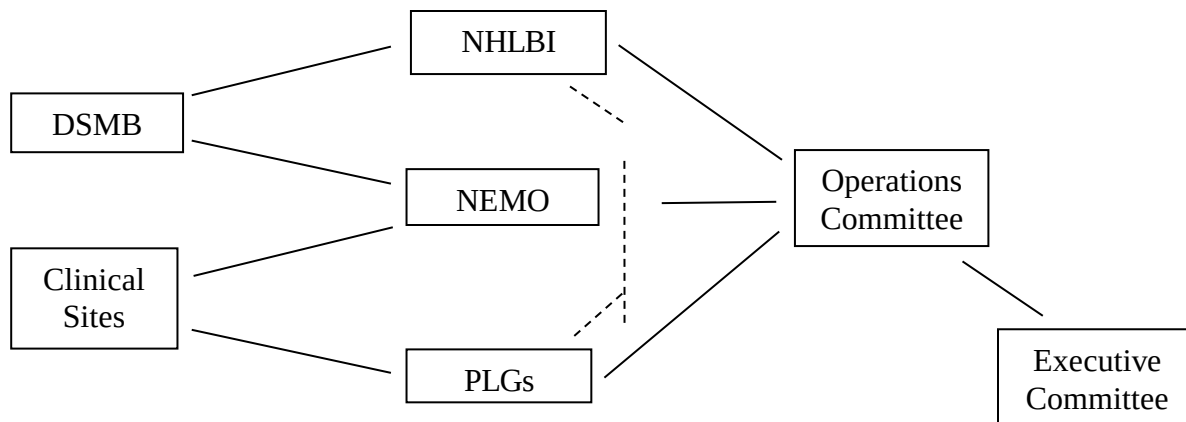
It is a dynamic document that may be updated throughout the course of the study to reflect any protocol or consent amendments or refinements in the case report form (CRF) or study procedures.

3.0 ORGANIZATION

The CleanUP-IPF trial is a collaborative effort involving the following groups:

1. National Institutes of Health
2. National Heart, Lung, and Blood Institute
3. University of Pittsburgh
4. Weill Cornell University
5. Duke Clinical Research Institute
6. Clinical Sites

The CleanUP-IPF leadership team shall be referred to as the “CleanUP-IPF Protocol Leadership Group” (PLG). The CleanUP-IPF PLG is one of multiple PLGs which comprise the Pulmonary Trials Cooperative (PTC). The following flow chart depicts each group which makes up the PTC:



Organizational Components

- Protocol Leadership Groups (PLGs) – design and carry out clinical studies
- Network Management Core (NEMO) – facilitate the research conducted by the PTC
- Operations Committee – primary responsibility for the implementation, oversight, and continuing evaluation of PTC studies
- Executive Committee – provide leadership and oversight to the PTC at large
- Clinical Sites – recruit and enroll participants, deliver the study intervention, complete clinic visits and phone calls, collect and enter data, and carry out procedures as defined by each study’s protocol
- Data and Safety Monitoring Board (DSMB) – review the design of each study, monitor patient safety, and review progress
- NHLBI Project Office – oversight for the whole endeavor

More information about the PTC and CleanUP-IPF can be found at ...

<http://www.pulmonarytrials.org/>

<https://clinicaltrials.gov/ct2/show/NCT02759120>

4.0 START-UP PROCEDURES

Start-up procedures for the CleanUP-IPF trial will be conducted and completed by the NEMO. The CleanUP-IPF PLG and DCRI have collaborated with the NEMO to create a “Site Green Light Letter,” which will be utilized to ensure each site has met all requirements prior to being activated by the NEMO. The “Site Green Light Letter” also includes a listing of all trainings and certifications modules that each site must complete via the PTC web portal.

5.0 SCREENING, BASELINE, AND RANDOMIZATION

5.1 Definitions of Subject Statuses

In the PTC there are a few events that form key milestones as candidates are considered for participation in a study: **initial contact, informed consent, and randomization**. Within the parameters of these milestones, the following status categories may be defined.

Pre-screening in the PTC is defined as any screening activity that occurs prior to actual contact with the potential participant. Chart reviews, registry scans, and physician referrals are all considered to be pre-screening. Any candidates who are disqualified during this activity are not included in the reporting requirements of the PTC.

Screening begins at the time of **initial contact with a candidate**, whether in written or verbal form. Screening includes interviewing the candidate for basic inclusion and exclusion criteria, and establishing the candidate’s ability to participate in the study.

Informed consent occurs during screening, a candidate may voluntarily withdraw from consideration, or may be found to be ineligible for the study. In these cases re-screening may occur, and it is the responsibility of the DCC to define the procedures, timing, and limitations for re-screening.

The DCC is required to report to the DSMB the number of people screened for the study. For the PTC, this number will include re-screenings, i.e. one person may be counted more than once as a screening for the study. Therefore whether re-screened candidates are tracked to identify multiple screenings is a DCC decision and does not affect reporting to the DSMB.

In studies with fairly basic inclusion and exclusion criteria, screening can be completed without first obtaining informed consent. Other studies, however, may require screening procedures that cannot be done without consent.

Enrollment is defined in the PTC as the **act of signing informed consent**. Although in some studies the term “enrolled” is used only for randomized participants, many IRB and also the PTC’s DSMB reporting requirements consider any candidate who has signed informed consent to be enrolled. Thus, enrolled participants may be found to be ineligible, they may withdraw during screening, or they may go on to randomization.

Eligibility is based on criteria established at many points in the screening and enrollment process. Candidates may be found to be ineligible during screening prior to consent, during more extensive screening after consenting, or during baseline measures deemed necessary for confirming final eligibility prior to randomization.

Candidates may voluntarily withdraw at any time during the screening process, but these are not considered to be ineligible. In DSMB reporting, these candidates are classified as “declined to participate.”

Eligibility is established only when all inclusion criteria are met, no exclusion criteria have been met, and the participant has confirmed willingness to be randomized for the study.

Randomization is defined as assigning an intervention to an eligible patient. It does not reference a specific subject visit.

5.2 Screening

After providing informed consent and signing the informed consent form (ICF), patients will be evaluated (via a physical examination) for eligibility into the study by ensuring that they:

- Are the appropriate age
- Have been diagnosed at the site with idiopathic pulmonary fibrosis
- Are not currently on antibiotic therapy, for treatment purposes (antibiotic prophylaxis for procedures do not meet criteria, nor do antivirals), and do not have any contraindications to antibiotic therapy.

Prior to randomization, the coordinator will document the following:

- Date of consent
- Patient characteristics (sex, race, ethnicity, age, height, weight)
- Information on how IPF diagnosis was made
- Known co-morbidities
- Details on patient history of gastroesophageal reflux disease (GERD)
- Physical exam findings
- Current concomitant medications
- Urine dipstick pregnancy test (for pre-menopausal female participants only)
- In recipients randomized to co-trimoxazole and taking digoxin, these recipients should be notified of a possible drug interaction and have additional digoxin monitoring by the provider monitoring digoxin levels for the patient.

- In recipients randomized to co-trimoxazole and taking warfarin, these recipients should be notified of a possible drug interaction and have additional coagulation (defined as PT/PTT/INR) monitoring by the provider monitoring coagulation labs for the patient.
- In recipients randomized to doxycycline and Vitamin A or retinoids, patients should be notified of a drug interaction and must stop these medications prior to starting doxycycline.
- Evaluation of seizure disorder and need for antiepileptic therapy. Antiepileptic therapy is a contraindication for enrollment.

The following procedures will be performed prior to randomization, if results are not available from recent clinically indicated testing:

- Spirometry and DLCO assessments, if not done within 90 days of randomization for clinical purposes.. The results of these tests will be recorded by the coordinator into the EDC system.
- Quality of life questionnaires
- Buccal and fecal sample collection for microbial ecology. Subjects will be given a fecal collection sample kit and instructions to take home.
- Urine pregnancy test for females who are able to become pregnant
- Blood draw for the following lab tests (**Described in Appendix B**):
 - Genotype
 - Gene expression
 - Chemistry panel and liver function tests– defined as minimum of sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), and creatinine, total bilirubin, direct bilirubin, alkaline phosphatase (ALP), alanine transaminase (ALT), and aspartate aminotransferase (AST)
 - Complete Blood Count (CBC)

If a subject does not meet the eligibility criteria due to a condition that subsequently resolves (e.g., infection or renal insufficiency), they may be considered for enrollment once the condition resolves if they meet the all eligibility criteria at the time of randomization.

5.4 Randomization

After providing informed consent and signing the ICF, all eligible study subjects will be randomized in a 1:1 allocation ratio to either receive or not receive a prescription drug voucher for daily antimicrobial therapy. Folic acid will also be included within the prescription drug voucher, for subjects randomized to co-trimoxazole therapy. Subjects should begin administration of drug without delay following randomization.

6.0 TREATMENT INTERVENTIONS AND DELIVERY

6.1 Treatment Interventions

This will be an unblinded, randomized clinical trial comparing the following treatment strategies

- Standard care
- Standard care + oral antimicrobial therapy

Patients randomized to receive antimicrobial therapy will receive a prescription drug voucher for the medication (and folic acid if given co-trimoxazole) during the enrollment visit. To minimize risk to the participating subject and to maximize a positive outcome we have created an algorithm for antimicrobial therapy that encourages use of co-trimoxazole but allows doxycycline use.

Figure 1 illustrates the proposed antimicrobial therapy algorithm. Contraindications to co-trimoxazole at enrollment include:

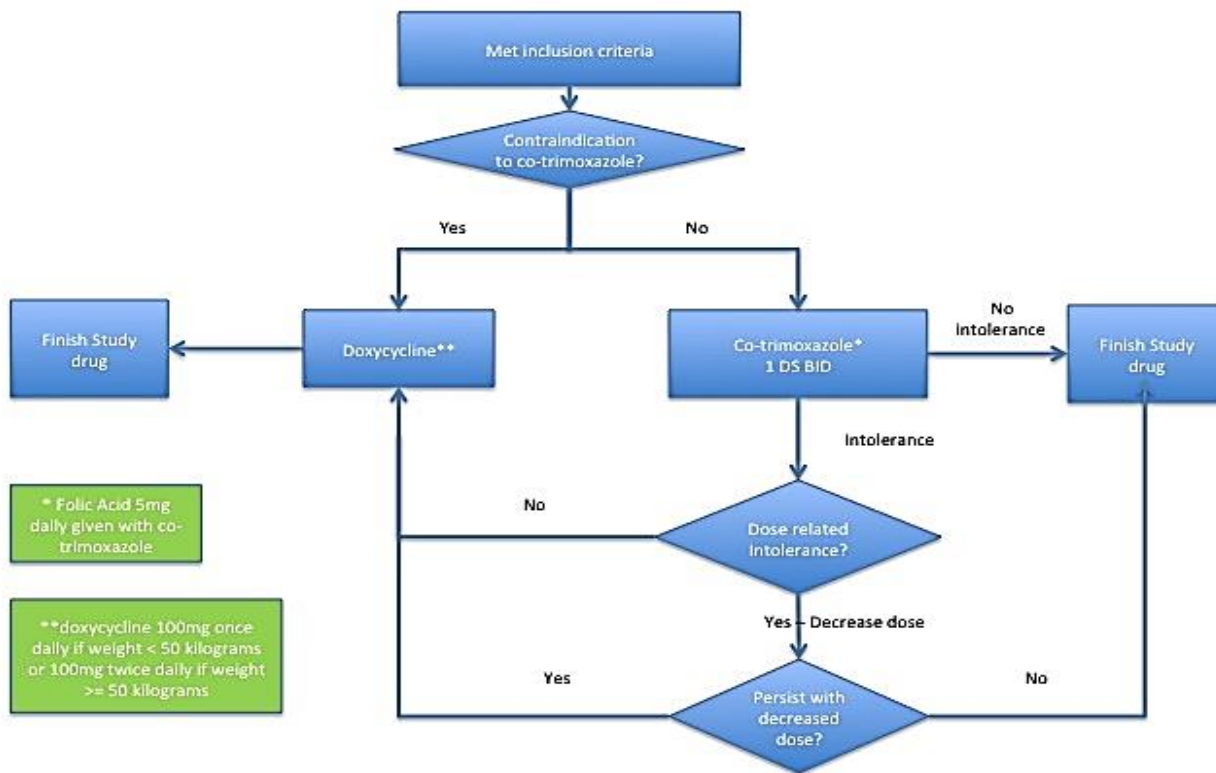
- allergy to sulfa products or trimethoprim
- renal insufficiency (GFR < 30 mL/min, defined as estimated from the blood urea nitrogen and creatinine)
- hyperkalemic (potassium > 5 mEq/L)
- concomitantly taking an ACEI, ARB, potassium sparing diuretic, dofetilide, methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide
- Other contraindication to co-trimoxazole in the investigator's opinion

Subjects meeting any of the above and randomized to antibiotic therapy will take doxycycline instead.

Subjects on vitamin A or retinoids will need to stop these medications if randomized to doxycycline.

Co-trimoxazole intolerance is defined by the investigator. Mild intolerance (e.g. nausea, abdominal pain, headaches, anorexia) may require a dose adjustment to half dose. Moderate intolerance (e.g. decreased leukocytes, mild increase in potassium) require a dose adjustment or a switch to doxycycline at the investigator's discretion. A significant intolerance (e.g. leukopenia, hyperkalemia, a decrease in GFR by more than 50% or to less than 30 ml/min, rash) requires stopping the co-trimoxazole and providing medical treatment as appropriate. Doxycycline should be started when medically appropriate in the opinion of the investigator after moderate or significant intolerance. All dose adjustments will be at the discretion of the treating physician(s) with the medical monitor available for consultation if needed. Dosing adjustments, and/or switching of co-trimoxazole to doxycycline, will be documented within the eCRFs, as well as the reason for the adjustment.

Figure 1



6.2 Randomization

All patients will be randomized using the study electronic data capture (EDC) system. Patients will be randomized to treatment in a 1:1 allocation ratio using a simple randomization scheme.

6.3 Blinding

In keeping with a pragmatic study design, this study will be unblinded. Blinding would add substantial additional complexity without commensurate incremental benefit related to testing the primary hypothesis of a treatment strategy trial.

6.4 Patient Safety and Concomitant Medications

This study will evaluate and compare treatment strategies of standard care and standard care + antimicrobial therapy in patients with IPF.

Although investigators are encouraged to follow the assigned treatment strategy for the study duration, in all

cases the patient's safety based on the clinical judgment of the treating physician will take priority over the specific treatment assignment.

There is the potential of adverse cardiovascular events secondary to co-trimoxazole therapy; this is felt to possibly reflect a drug interaction with trimethoprim resulting in hyperkalemia^{8,9}. Review of older literature suggests that the major risk factors for trimethoprim related hyperkalemia are higher trimethoprim dose and renal insufficiency with hypoaldosteronism, and potassium altering medications and age as probable risk factors¹⁰. Our inclusion/exclusion criteria should mitigate this risk as will monitoring for hyperkalemia early after the introduction of co-trimoxazole therapy¹⁰.

If a subject randomized to the antimicrobial strategy group develops an intolerance to co-trimoxazole the dosage should first be decreased to one double strength 160mg trimethoprim/ 800mg sulfamethoxazole (co-trimoxazole) three times weekly plus folic acid 5 mg daily. If intolerance continues with co-trimoxazole then the antimicrobial agent can be changed to doxycycline (with no 5mg folic acid).

Doxycycline will be dosed at 100 mg once daily if body weight is < 50 kg and 100 mg twice daily if $\geq$ 50 kg, and no 5mg folic acid will be prescribed.

6.5 Pharmaceutical Drug and Distribution Services

Local pharmacies will be used to supply study participants with drug. No sites will store CleanUP-IPF study drugs of any kind.

A drug voucher system, called TrialCard, will be utilized to issue drug voucher cards to subjects. These vouchers will be pre-loaded with funds which the subjects will redeem at their local pharmacy to cover any out-of-pocket costs of the study drug to which they are randomized.

TrialCard will ship the drug voucher cards to Investigator Site Study Coordinators. The site's PI will then determine if each subject is eligible to participate in the trial. For those subjects randomized into the intervention group, the PI will prescribe the appropriate medication(s) to the subject and provide the subject with a valid prescription and voucher card. The subject will take the voucher card and prescription to a local pharmacy and present both to the pharmacist. The pharmacist will then fill the prescription(s) and use the voucher card as the method of payment. TrialCard's processor will adjudicate the claim and complete the transaction.

Only one drug voucher card should be issued to each subject over the lifetime of the trial, however each voucher card may be redeemed for multiple uses.

TrialCard will supply the CleanUP-IPF PLG with card utilization and adherence reports.

7.0 FOLLOW-UP EVALUATIONS

All study participants will continue to be followed on a usual care basis. Refer to the schedule of assessments for more details. Study participants will be followed for up to a maximum of 36 months. It is anticipated that the overall study will end once the final enrolled patient completes their 12-month visit. Subjects randomized

to antimicrobial therapy will remain on the assigned therapy until the end of the study or their 36-month study visit. Study participants are encouraged to contact their treating pulmonologist regarding their use of anti-microbial therapy after their study participation has ended. At the completion of the 36-month phone contact data collection will cease. To gain a better understanding of the long-term consequences of treatment, patients may be contacted up to 5 years after the end of their study participation. The primary analyses will be based on data collected until the end of the active treatment portion of the study.

7.1 One (1) week lab (Co-trimoxazole assigned subjects ONLY)

Approximately 1 week (visit window of 1 week +/- 3 days) after enrollment (and the beginning of administration of drug), subjects assigned to the antimicrobial therapy arm will return to the enrolling site or a local laboratory for the following:

- Blood drawn for electrolytes (**Described in Appendix B**)

7.2 One (1) month phone contact

Approximately 1 month (visit window of 1 month +/- 7 days) after enrollment, all subjects will be contacted by the site coordinator to document the following:

- Any issues related to drug assignment
- Vital status assessment
- Medication adherence
- Hospitalization and respiratory infection assessment

7.3 Three (3) month lab for antimicrobial assigned subjects ONLY

Approximately 3 months (visit window of 3 months +/- 7 days) after enrollment, subjects assigned to the antimicrobial therapy arm will return to the enrolling site or a local laboratory for the following:

- Blood draw for the following safety labs (**Described in Appendix B**):
 - Chemistry panel and liver function tests– defined as minimum of sodium, potassium, chloride, bicarbonate, BUN, and creatinine, total bilirubin, direct bilirubin, alkaline phosphatase, ALT, and AST
 - Complete blood count (CBC)

7.4 Six (6) month lab for antimicrobial assigned subjects ONLY

Approximately 6 months (visit window of 6 months +/- 7 days) after enrollment, subjects assigned to the antimicrobial therapy arm will return to the enrolling site or a local laboratory for the following:

- Blood drawn for the following safety labs (**Described in Appendix B**):
 - Chemistry panel and liver function tests– defined as minimum of sodium, potassium, chloride, bicarbonate, BUN, and creatinine, total bilirubin, direct bilirubin, alkaline phosphatase, ALT, and AST

- Complete blood count (CBC)
- Vital status Assessment
- Medication adherence
- Hospitalization and respiratory infection information

7.5 Six (6) month phone contact (for standard care arm)

Approximately 6 months (visit window of 6 months +/- 4 weeks) after enrollment, subjects randomized to the standard care arm **ONLY** will be contacted by the site coordinator to document the following:

- Vital status assessment
- Medication adherence
- Hospitalization and respiratory infection information

7.6 Twelve (12) month in-person visit

All subjects will return to the enrolling site approximately 12 months (visit window of 12 months +/- 4 weeks) after enrollment and will complete the following:

- Quality-of-life questionnaires
- Spirometry and DLCO assessment
 - *If a spirometry (with DLCO) assessment is available within 90 days of the in-person visit it may be used as the study assessment. Otherwise the spirometry assessment with DLCO should be conducted at the in-person visit.
- Blood draw for the following safety labs (for antimicrobial arm only):
 - Chemistry panel and liver function tests– defined as minimum of sodium, potassium, chloride, bicarbonate, BUN, and creatinine, total bilirubin, direct bilirubin, alkaline phosphatase, ALT, and AST
- Complete Blood Count (CBC) (for antimicrobial arm only)
- Blood draw for gene expression
- Buccal and fecal samples collection for microbial ecology

7.7 Eighteen (18) month phone contact

Approximately 18 months (visit window of 18 months +/- 4 weeks) after enrollment, all subjects will be contacted by the site coordinator to document the following:

- Vital status
- Medication adherence
- Hospitalization and respiratory infection information

7.8 Twenty-four (24) month in-person visit

All subjects will return to the enrolling site approximately 24 months (visit window of 24 months +/- 4 weeks) after enrollment and will complete the following:

- Quality-of-life questionnaires
- Spirometry and an DLCO assessment
 - *If a spirometry (with DLCO) assessment is available within 90 days of the in-person visit it may be used as the study assessment. Otherwise the spirometry assessment with DLCO should be conducted at the in-person visit.
- Blood draw for the following safety labs (for antimicrobial arm only):
 - Chemistry panel and liver function tests– defined as minimum of sodium, potassium, chloride, bicarbonate, BUN, and creatinine, total bilirubin, direct bilirubin, alkaline phosphatase, ALT, and AST
- Complete Blood Count (CBC) (for antimicrobial arm only)
- Blood draw for gene expression
- Buccal and fecal samples collection for microbial ecology

7.9 Thirty (30) month phone contact

Approximately 30 months (visit window of 30 months +/- 4 weeks) after enrollment, subjects will be contacted by the site coordinator to document the following:

- Vital status
- Medication adherence
- Hospitalization and respiratory infection information

7.10 Thirty-six (36) month phone contact

Approximately 36 months (visit window of 36 months +/- 4 weeks) after enrollment, subjects will be contacted by the site coordinator to document the following:

- Vital status
- Medication adherence
- Hospitalization and respiratory infection information

Participants randomized to the antimicrobial arm who are still taking study drug at this visit should consult with their treating pulmonologist about continuing any prescriptions for antimicrobial therapies, as prescription drug voucher coverage will cease after completion of the 36 month phone contact. Data collection for study purposes will cease after completion of the 36-month phone contact.

7.11 Schedule of Assessments (on following page)

VISIT	V1	V1A ²	V2	V2A ³	V2B ³	V3	V4	V5	V6	V7	V8
	Screening/ Enrollment	1 Week (+/- 3 days)	1 Month (+/- 7 days)	3 Month (+/-7 days)	6 Month (+/-4 weeks)	6 Month (+/- 4 weeks)	12 Month (+/- 4 weeks)	18 Month (+/- 4 weeks)	24 Month (+/- 4 weeks)	30 Month (+/- 4 weeks)	36 Month (+/- 4 weeks)
Task			Phone Call			Phone Call		Phone Call		Phone Call	Phone Call
Informed Consent	X										
Physical Exam	X										
Medical History	X										
Randomization	X										
IPF Diagnosis Checklist	X										
Spirometry (if not available in last 90 days)	X						X		X		
DLCO (if not available in last 90 days)	X						X		X		
Concomitant Medication Review	X										
Concomitant Medication Update			X			X	X	X	X	X	X
Complete Blood Count (CBC)	X (if not available in last 90 days)						X ³		X ³		
Chemistry panel w/liver function tests	X (if not available in last 90 days)	X ²		X ³	X ³		X ³		X ³		
Electrolytes only											

Genotype	X										
Gene expression	X						X		X		
Buccal Swab, Fecal samples	X						X		X		
Patient Reported Outcomes Questionnaires ¹	X						X		X		
Clinical Events			X			X	X	X	X	X	X
Mortality			X			X	X	X	X	X	X
Hospitalization			X			X	X	X	X	X	X
Resp. infection											

8.0 DATA MANAGEMENT

8.1 Overview of Data Management

The DCRI will have primary responsibility for data management, including the development of data collection systems, data monitoring processes, and data storage and back up. State-of-the-art technology will be used for the management of the network's data.

8.2 Design and Development

The DCC will be responsible for development of the electronic case report forms (eCRFs), development and validation of the clinical study database, ensuring data integrity, and training clinical center staff on applicable data management procedures. A web-based distributed data entry model will be implemented. This system will be developed to ensure that guidelines and regulations surrounding the use of computerized systems used in clinical trials are upheld.

8.3 Data Collection Forms

The data collection process consists of direct data entry at the study clinical centers into the IBM Clinical Development study database. Data entry should be completed according to the instructions provided and project specific training. The investigator is responsible for maintaining accurate, complete and up-to-date records, and for ensuring the completion of the data collection forms for each research participant.

8.4 Data Acquisition and Entry

Data entry into eCRFs shall be performed by authorized individuals. Selected eCRFs may also require the investigator's written signature or electronic signature, as appropriate. Electronic CRFs will be monitored for completeness, accuracy, and attention to detail during the study. Data must be entered into the IBM Clinical Development system within 72 hours of subject visit completion.

8.5 Data Editing

Completed data will be entered into the IBM Clinical Development system. If incomplete and/or inaccurate data are found, a data query will be generated and distributed to clinical centers for a response. Clinical centers will resolve data inconsistencies and errors and enter all corrections and changes into the database. Data queries must be addressed/responded to within 48 hours of the time which they are issued to the site.

8.6 Data Security

Access to databases will be controlled centrally by the DCRI through user passwords linked to appropriate privileges. This protects the data from unauthorized changes and inadvertent loss or damage. Database and web servers will be secured by a firewall and through controlled physical access. Database back up will be performed daily using standard procedures in place at the DCRI. All disk drives that provide network services, and all user computers, will be protected using virus-scanning software.

9.0 STATISTICAL ANALYSIS

Means, standard deviations, medians, 25th and 75th percentiles will be presented for continuous variables; the number and frequency of patients in each category will be presented for nominal variables. Statistical tests with a two-sided p value <0.05 will be considered statistically significant, unless otherwise stated. Analyses will be performed using SAS software (SAS Institute, Inc., Cary, NC).

9.1 Analysis of Primary Endpoint

Detailed description of the plan for statistical analysis of each endpoint will be detailed in a Statistical Analysis Plan. The primary analysis will be based on intention to treat. Crossovers will be tracked and we will have an alternate analysis cohort based on these data. Subjects receiving lung transplantation will be censored for all endpoints at the time of transplantation.

The statistical comparison of the two randomized arms with respect to the primary endpoint will be a time-to-event analysis, and therefore will be based on the time from randomization to first non-elective, respiratory hospitalization or death from any cause. The Cox proportional hazards regression model will be the primary tool to analyze and assess outcome differences between the two treatment arms. The Cox model will include an indicator variable for treatment group, age, sex, baseline DLCO, baseline FVC, use of NAC at enrollment, and choice of antimicrobial agent prior to randomization. Hazard ratios and 95% confidence intervals will summarize the differences between treatment arms.

For the primary analysis, subjects without any respiratory hospitalization or death event at the time of analysis will be censored at their last visit or lung transplantation. The censoring mechanism is assumed to be non-informative. Supportive analyses will be performed to assess the impact of a potential informative censoring.

9.2 Analysis of Secondary Endpoints

The analyses for the time-to-event secondary endpoints will be similar to those outlined for the primary endpoint using the time from randomization through the first occurrence of any component of a specific secondary endpoint (or censoring) as the response variable, and assessing group differences using the Cox proportional hazards model. Analyses of continuous secondary outcome variables will rely on a repeated measures approach, using mixed models and incorporating all available assessments. The analyses of all study endpoints will be detailed in the Statistical Analysis plan.

10.0 SUBJECT SAFETY, SERIOUS ADVERSE EVENTS, UNANTICIPATED PROBLEMS, AND PROTOCOL DEVIATIONS

10.1 Role of the CleanUP-IPF Adjudication Committee

An Adjudication Committee will classify all hospitalization events. The Adjudication Committee will follow procedures described in the Adjudication Charter. Briefly, medical records from inpatient hospitalizations will be obtained by the data coordinating center through an established, secure process which will be detailed in the informed consent document. Non-elective respiratory hospitalizations will be defined as any unplanned inpatient hospitalizations for which the primary cause was a pulmonary condition, in the opinion of the blinded adjudicators and based on all available clinical data. Examples include, but are not limited to, the following:

- acute exacerbation of IPF (definite or suspected)
- pulmonary infection/pneumonia
- pulmonary embolus
- pneumothorax
- pulmonary aspiration
- ARDS of identifiable cause

These causes will be adjudicated by review of admission history and physical and discharge summary from the hospitalization. These documents will be obtained (with patient consent) by the DCC from the hospital where the encounter occurred. Documents will be made available to adjudicators in PDF form via the secure and integrated data management system (IBM Clinical Development Endpoint Adjudication Module) at the DCC. Each hospitalization event will be adjudicated by one of the study pulmonologists from the adjudication committee, ensuring that the adjudicator is independent from the study site at which the event occurred. If this adjudication is in agreement with the site investigator's assessment (with regard to date of event, elective vs. non-elective and respiratory vs. non-respiratory), this assessment will serve as the final event adjudication. In the event of the independent adjudicator's assessment disagreeing with the site investigator's assessment, a second blinded member of the adjudication committee, also independent of the involved site, will serve as a "tiebreaker".

Hospitalizations occurring primarily for lung transplantation will be considered "elective," as the timing of lung transplant events is unpredictable because of donor lung availability rather than occurrence of acute or worsening illness. On the other hand, hospitalizations initially caused by an acute pulmonary condition but during which lung transplantation later occurs will be considered non-elective. Non-pulmonary causes of dyspnea, such as cardiac disease, will not be considered respiratory causes of hospitalizations.

10.2 Adverse Events (AEs)

Adverse events (AEs) of special interest ONLY will be collected for the CleanUP-IPF trial. These AEs include:

- Arrhythmia
- Vomiting
- Diarrhea
- Rash
- Hyperkalemia

These adverse events of special interest will be collected via data entry into the eCRF within the electronic data capture system. Start and stop dates will also be collected for these events, as well as any concomitant medications prescribed (with start and stop dates of the concomitant medication) for treatment of such events.

10.3 Serious Adverse Events (SAEs)

Any adverse Event that meets any of the following criteria: (1) results in death; (2) is life-threatening (i.e. places a participant at immediate risk of death from the event as it occurred); (3) requires inpatient hospitalization or prolongation of existing hospitalization; (4) results in a persistent or significant disability/incapacity; (5) results in a congenital anomaly/birth defect; OR (6) any other adverse event that, based upon appropriate medical judgment, may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (e.g. allergic bronchospasm requiring intensive treatment in the emergency room or at home).

Information about all serious adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on the Serious Adverse Event eCRF.

For this study, all SAEs occurring from the time of drug administration to 30 days post-study completion visit will be captured on the SAE eCRF. As the Month 36 Visit is a Phone Call Visit, review of subjects' medical records is required, in order to evaluate any SAEs within 30 days post-study completion visit. Unless exempted as described below, all SAEs, whether or not deemed drug-related, must be reported by the investigator or qualified designee within 1 business day of first becoming aware of the event. The investigator/qualified designee will enter the required information regarding the SAE into the appropriate module of the IBM Clinical Development, which will automatically result in distribution of the information to the Duke Clinical Research Institute Medical Monitor and Clinical Operations team, and the Network Management Core (NEMO). If IBM Clinical Development is temporarily unavailable, the event, including the investigator-determined causality to study drug, should be reported via a paper back-up SAE form to the DCRI Medical Monitor and Clinical Operations team, and the NEMO. Upon return of the availability of EDC system, the SAE information must be entered into the eCRF.

Follow-up: When additional relevant information becomes available, the Investigator will record follow-up information according to the same process used for reporting the initial event as described above. The Investigator will follow all reportable events until resolution, stabilization or the event is otherwise explained.

Investigators are also responsible for promptly reporting SAEs to their reviewing IRB/EC in accordance with local requirements.

The DCRI Medical Monitor and Clinical Operations team, and NEMO will follow all SAEs until resolution, stabilization, until otherwise explained or until the last subject completes the final follow-up, whichever occurs first. The DCRI Medical Monitor and Clinical Operations team will report all SAEs to the CleanUP-IPF trial team within 1-2 business day(s) of receipt and notify the Data Safety Monitoring Board (DSMB) chair monthly. If no events have occurred, the DCRI Clinical Operations team will notify the NEMO, and NEMO will notify the DSMB chair as such.

An independent DSMB will review composite data at regular intervals throughout the study. The DSMB will be empowered to stop the study for evidence of efficacy or harm.

Events Relatedness refers to the extent to which an adverse event is considered to be related to the intervention or study procedures. An adverse event is considered related if there is a reasonable possibility that the event may have been caused by the procedure. The following definitions apply to relatedness, per the Pulmonary Trials Cooperative's Manual of Operations:

- 1) Unrelated: adverse event is clearly due to extraneous causes (e.g., underlying disease, environment)
- 2) Unlikely: (adverse event **must meet 2** of the following criteria):
 - Does not have temporal relationship to intervention
 - Could readily have been produced by the participant's clinical state
 - Could have been due to environmental or other interventions
 - Does not follow known pattern of response to intervention
 - Does not reappear or worsen with reintroduction of intervention
- 3) Possible: (adverse event **must meet 2** of the following criteria):
 - Has a reasonable temporal relationship to intervention
 - Could not readily have been produced by the participant's clinical state
 - Could not readily have been due to environmental or other interventions
 - Follows a known pattern of response to intervention
- 4) Probable: (adverse event **must meet 3** of the following criteria):
 - Has a reasonable temporal relationship to intervention
 - Could not readily have been produced by the participant's clinical state or have been due to environmental or other interventions
 - Follows a known pattern of response to intervention
 - Disappears or decreases with reduction in dose or cessation of intervention
- 5) Definite: (adverse event **must meet 4** of the following criteria):
 - Has a reasonable temporal relationship to intervention
 - Could not readily have been produced by the participant's clinical state or have been due to environmental or other interventions

- Follows a known pattern of response to intervention
- Disappears or decreases with reduction in dose or cessation of intervention and recurs with re-exposure

10.4 Pregnancy

Pregnancy occurring during a clinical investigation, although not considered a serious adverse event, must be reported to DCRI within the same timelines as a SAEs. The pregnancy will be recorded on the appropriate paper pregnancy tracking form. The pregnancy will be followed until final outcome. Any associated SAEs that occur to the mother or fetus/child will be recorded in the SAE eCRF, within IBM Clinical Development.

All pre-menopausal female participants will have a urine sample collected at their screening/baseline visit, and a urine dipstick (UDS) pregnancy test will be completed. Clinical sites are responsible for providing their own UDS tests for utilization in the trial, as the CleanUP PLG will not be supplying these for the study.

In an effort to prevent pregnancies from occurring during a subject's participation in the study, women of child-bearing potential must use two acceptable methods of contraception at the same time unless the subject has had a surgical sterilization, in which case no additional contraception is required. Medically acceptable contraceptives include: (1) documented surgical sterilization (such as a hysterectomy, tubal ligation), (2) barrier methods (such as a condom or diaphragm) used with a spermicide, (3) hormonal contraception (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring) or (4) an intrauterine device (IUD) or intrauterine system (IUS). Abstinence is not an acceptable form of contraception in this study.

Male participants must also agree to take all necessary measures to avoid causing pregnancy in their sexual partners during the study. Medically acceptable contraceptives include: (1) surgical sterilization (such as a vasectomy), or (2) a condom used with a spermicidal. Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use.

10.4 Unanticipated Problems (UPs)

Any incident, experience, or outcome that meets **ALL** of the following criteria:

- Unexpected in terms of nature, severity, or frequency, taking protocol research procedures and participation population characteristics into consideration
- Related or possibly related to a person's participation in the research.
- Possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research
- Places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

Examples of unanticipated problems may include both non-medical and medical problems:

- Medical problems: incorrect medication or dosage administered; contaminated or expired study medications; laboratory equipment malfunctions. **Note that these do not require a patient having a medical reaction to the error.**
- Non-medical problems: breach of confidentiality; inadvertent loss of study records; privacy violation.

Unanticipated Problems may lead to adverse medical events for some participants. These adverse events or serious adverse events should be reported based on standard study protocol for AE and SAE reporting.

10.5 Protocol Deviations (PDs)

Any change, divergence, or departure from the IRB-approved research protocol is termed as a protocol deviation. The impact of a protocol deviation is characterized by designation as serious or not serious.

Examples of **not serious** Protocol deviations include, but are not limited to:

- Scheduling a protocol visit slightly outside of the timing in the protocol, but at a time that would not compromise the interpretation of the study data or impact the health of the participant
- Inability to obtain a sample that is needed for exploratory analysis that does not impact the health of the participant
- Protocol specifications for clinical testing are not followed

Examples of **serious** Protocol Deviations:

- The deviation has harmed or posed a significant or substantive risk of harm to the research participant. Examples include, but are not limited to: a research participant received the wrong treatment or incorrect dose or a research participant received an excluded concomitant medication
- The deviation compromised the scientific integrity of the data collected for the study. Examples include, but are not limited to: a research participant was enrolled but does not meet the protocol's eligibility criteria or changing the protocol without prior IRB approval, and/or subject randomized prior to completion of baseline quality of life assessments.
- The deviation is a breach of human participant protection regulations, or NIH policies or procedures. Examples include, but are not limited to: failure to obtain informed consent prior to initiation or study-related procedures, performing tests or procedures beyond those anticipated in the protocol or by those not approved to perform such actions by the IRB, or falsifying research or medical records
- The deviation involves a serious or continuing noncompliance with applicable federal, state, local or institutional human participant protection laws, regulations, or policies, or procedures. Examples include, but are not limited to: working under an expired professional license or certification, failure to follow federal and/or local regulations, and intermural research or NIH Clinical Center policies, repeated protocol deviations (i.e., a study site repeatedly performing a study assessment incorrectly despite recognition of the problem)
- The deviation is inconsistent with the NIH Human Research Protection Program (HRPP) research, medical, and ethical principles. Examples include, but are not limited to: a breach of confidentiality and/or privacy, or inadequate or improper informed consent procedures

Some serious protocol deviations may place the participant at greater risk of physical or psychological harm. In such cases, the event should be reported as an unanticipated problem.

10.6 Non-Compliance

Noncompliance is defined as the failure to comply with applicable NIH HRPP policies, IRB requirements, or regulatory requirements for the protection of human research participants. There are three types of non-compliance, they are:

- Serious non-compliance: Non-compliance that: increases risks, or causes harm, to participants, decreases potential benefits to participants, compromises the integrity of the NIH HRPP, invalidates the study data
- Continuing non-compliance: Non-compliance that is recurring. It could also include a failure to respond to IRB requests to resolve previous allegations of non-compliance
- Minor (non-serious) non-compliance: Non-compliance that, is neither serious nor continuing

10.7 Expedited Reporting

Site PIs are required to promptly report all serious adverse events (SAEs) and unanticipated problems (UPs) to the study DCC, including an assessment of relatedness and expectedness. Unexpected and related serious adverse events and all unexpected problems require expedited reporting to regulatory agencies.

Figure 1 describes the process site PIs should follow in classifying adverse events and unanticipated problems, and in determining the action required. Events are clearly labeled as those that require Systematic Reporting (SR) and those that also require Expedited Reporting (ER).

Systematic Reporting (SR) Procedures

All adverse events (serious and non-serious) and unanticipated problems must be reported to the DSMB and NEMO on a regularly scheduled basis (such as the semi-annual DSMB meetings and as data for the NEMO quarterly reports). This includes events and problems previously reported through expedited reporting.

Expedited Reporting (ER) Procedures

There are three classes of events that need to be reported in an expedited manner. These are also presented in **Figure 1**:

- Fatal or life threatening unexpected SAEs that are possibly, probably or definitely related to the research study
- Non-fatal, non-life threatening unexpected SAEs that are possibly, probably or definitely related to the research study
- Unanticipated problems

The process for expedited SAE reporting is summarized in **Figure 2**. The assigned study staff member should fill out an SAE form whenever the event is deemed serious in nature. In cases where the event is not serious but places the participant at greater risk of physical or psychological harm, and is both unexpected and possibly related to the study, the assigned study staff member should fill out an Unanticipated Problem (UP) form. The process for expedited reporting for UPs is summarized in **Figure 3**.

The completed SAE and UP forms should be sent to DCRI (via data entry into the appropriate eCRF page) within 24 hours of acknowledging the event. When an unexpected SAE has been reported, the DCRI Clinical Operations team and/or DCRI Data Management will forward the SAE form along with relevant patient

history such as comorbidities, to the DCRI CleanUP Medical Monitor (and DCRI Clinical Events Classification team, if applicable) for review and adjudication.

Following the Medical Monitor's feedback on the expectedness and relatedness of the SAE, the DCRI Medical Monitor will complete an SAE report incorporating the event details and the Medical Monitor's feedback.

When a UP or SAE requiring expedited reporting occurs, the data are to be collected and reported to the NEMO within established timeframes presented in Figures 2 and 3. To make it easier for the DSMB to review reports from all studies, SAE and UP event reporting templates have been developed, and are available on the PTC web portal. Reports should be sent to the NEMO by uploading them to the PLG Reports CloudShare on the PTC website. The NEMO will be responsible for forwarding the report to the NHLBI and the DSMB. The DCRI Clinical Operations team should also send the report to the Site PI for use in reporting to local IRBs as required.

Upon receipt of the expedited report, the DSMB members will decide whether the event should be either a) discussed at the next scheduled DSMB meeting or b) discussed as soon as possible at an ad hoc meeting.

The NHLBI Executive Secretary will inform the NEMO about the decisions made by the DSMB related to this SAE or UP event (i.e. whether an ad hoc meeting to discuss the event occurred, and any decisions from that meeting). The NEMO will then send the DSMB response to the DCRI team and to the Site PI.

Figure 1: Event Reporting Flowchart

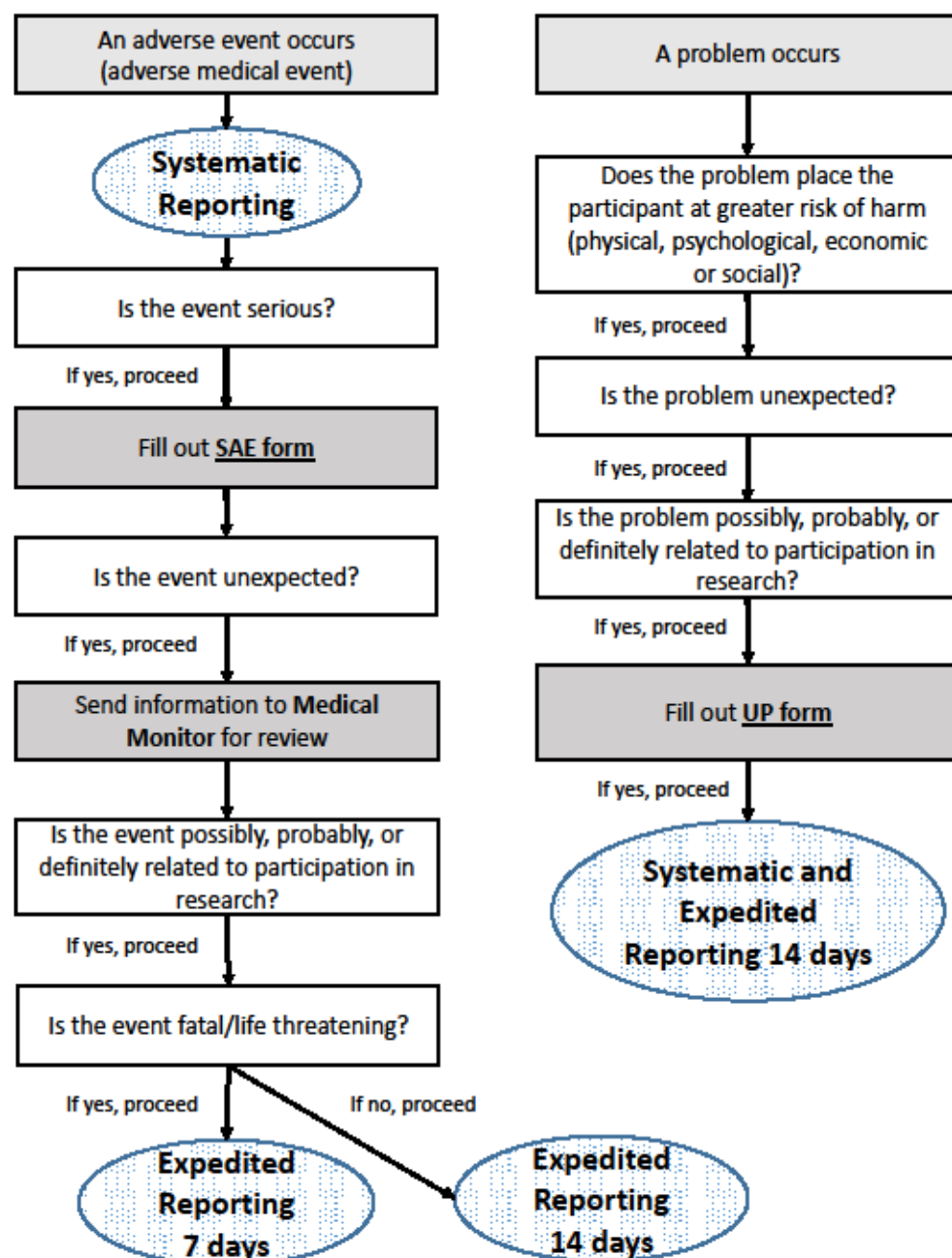


Figure 2: Steps in expedited reporting of SAEs

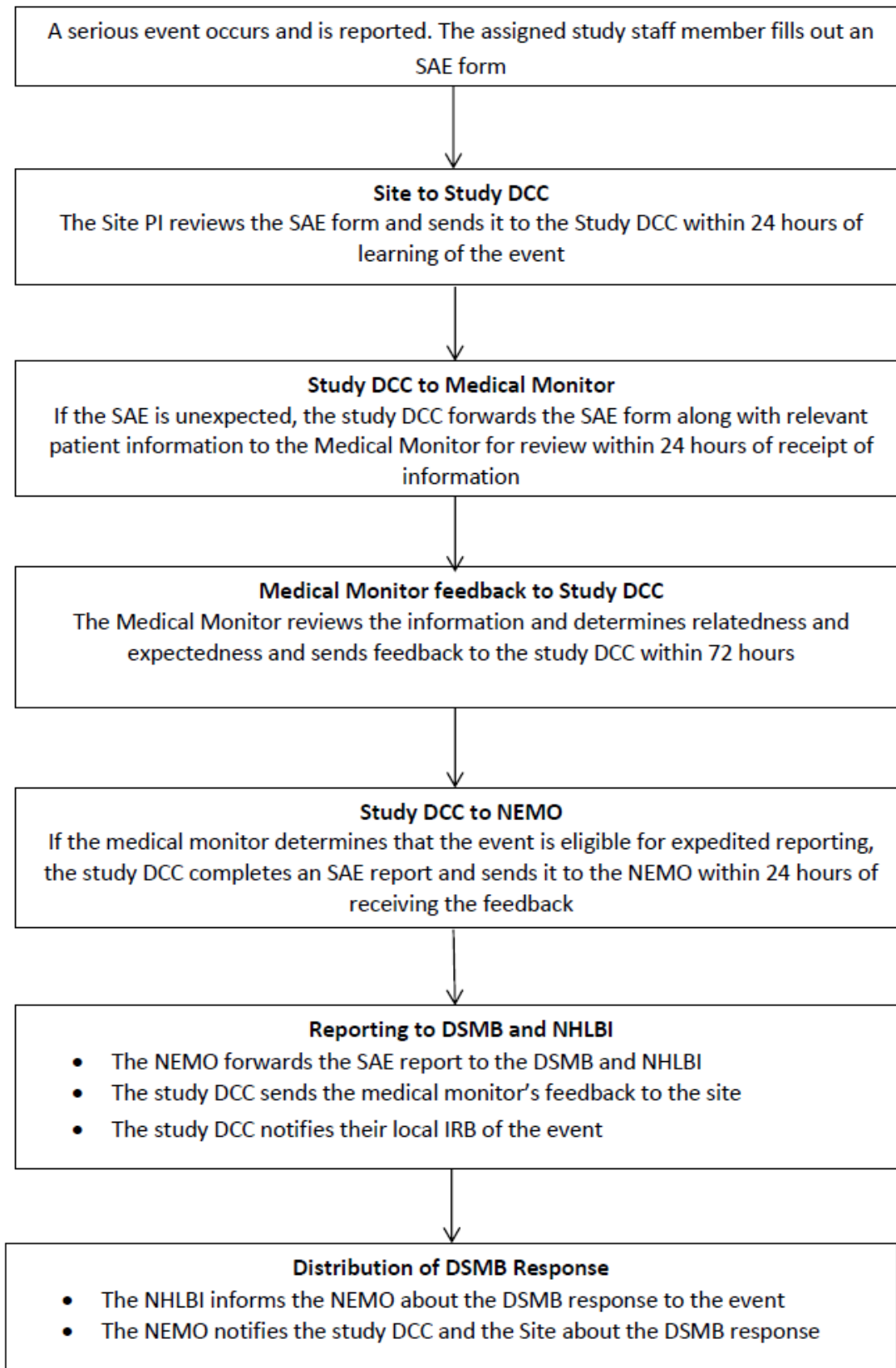
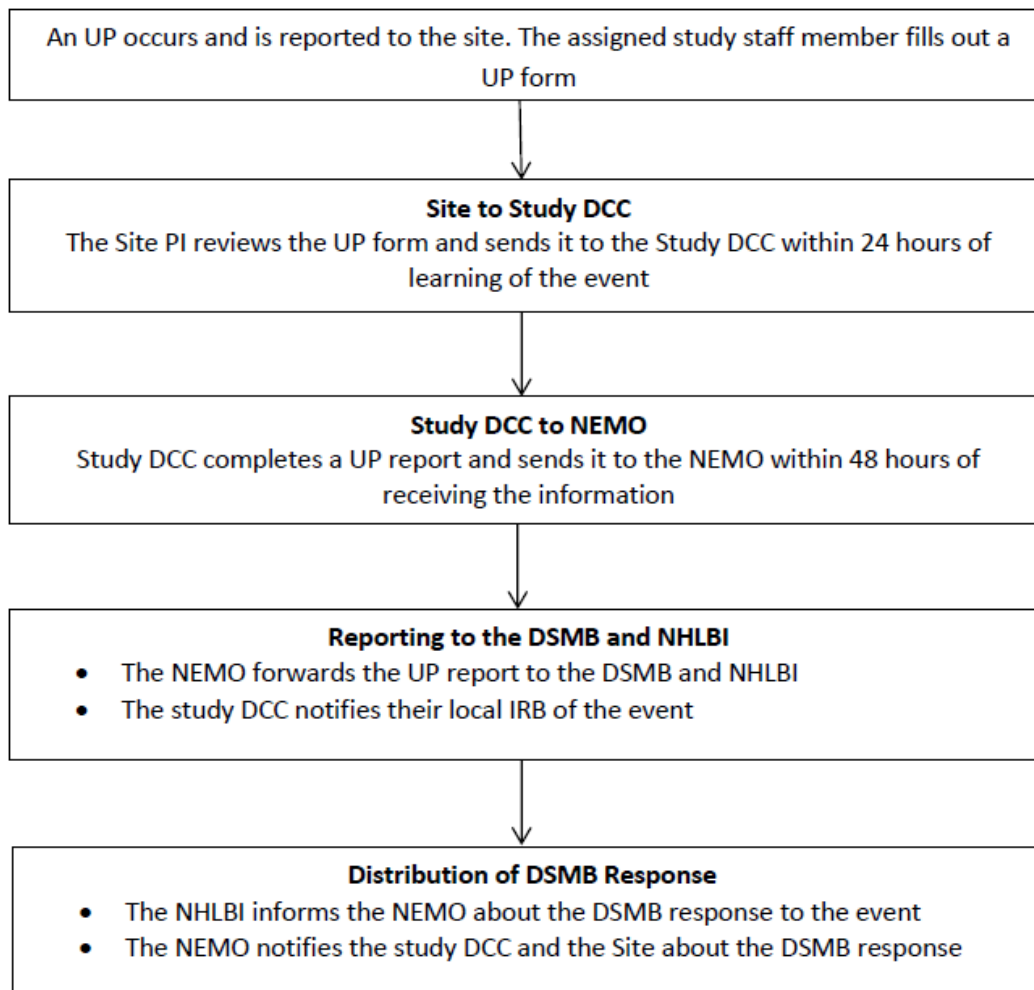


Figure 3: Steps in expedited reporting of UPs



11.0 COMMUNICATIONS

11.1 Website

The NEMO created and maintains a PTC website consisting of a Public section available to anyone and a password-protected Researcher section available only to those granted access.

11.1.1 Publicly Accessible Section

The Public PTC website is located at www.pulmonarytrials.org. It is geared towards three audiences: potential participants in PTC studies and other interested in the research and treatment of pulmonary disease; potential clinical site investigators; and research groups interested in becoming a PLG. The content is crafted to increase the site's prominence in search engines while remaining informative and accurate.

The main page and some other sections of the Public PTC website contain information about the Cooperative as a whole. These sections include basic information about the purpose of the PTC, the diseases that are being studied, a general overview of the current studies, and information for potential clinical trial participants.

Each current PTC study has a section within the Public website with a similar look-and-feel and content. These sections are where potential participants can find details about the research, basic eligibility criteria, a map of the clinical sites, and contact information for each clinical site. There are also sections for study news and researcher biographies.

11.1.2 Researcher Site

The Researcher website can be reached directly or through the Public site. It is a tool to help the NEMO, PLGs, Clinical Sites, and NHLBI stay organized and meet the goals of the PTC.

Access to the Researcher website is granted after the NEMO approves a request (consulting with the PLG or Clinical Site if needed), at which time the user is assigned a username and password along with a researcher ID. Based on the user's roles, access to certain areas may be restricted. For example, a CT technician does not have access to data entry systems, and a Coordinator working on multiple studies has access to each, but does not have access to sections dedicated to other studies.

Most areas of the Researcher website have a section for the PTC as a whole and for each current study. Each PLG selects which members of its staff have administrative privileges over these areas. The areas include:

- Document Sharing, where important documents like Operations Memos and Protocol modifications can be shared.
- Calendar, where upcoming meetings and calls are listed.
- Directory, which is sortable and includes distribution lists for Committees and Working Groups
- Help Center, for technical issues, eligibility questions, etc.

- Training and Certification, where clinical site staff can access training documents and take certification quizzes.
- PLG Reporting, to enable secure data and report transfer between the NEMO and the PLGs.

Each PLG also has an area with link(s) to its data management system(s). These pages can be seen only by those who are working on that study and have the appropriate user roles. The links take users to the page for the data management system, where they are required to log in again with the credentials assigned for that system.

11.2 Newsletters

The NEMO sends newsletters to clinical sites on a monthly schedule containing updates and information about the PTC as a whole. PTC newsletters also include major updates from each study, such as recruitment milestones and protocol modifications. An archive of past newsletters is available on the website.

The CleanUP PLG will send sites a bi-weekly Enrollment Poster with updates regarding study and site enrollment metrics, data reminders, important dates to remember, etc. The Enrollment Poster will be distributed to sites on approximately the first and fifteenth day of each month.

11.3 External Communication: Media

When entities within the PTC want to invite media coverage to their work, approval must be sought by three entities—the institutions involved in the research, the NHLBI, and the Operations Committee of the PTC.

In the case that individuals involved with the PTC are asked for information by an external person or entity, the PTC staff or investigator must notify the communications officer at their institution, the PTC Operations Committee and the NHLBI prior to agreeing to share information.

12.0 PUBLICATION POLICIES AND PROCEDURES

12.1 Presentations and Abstracts

12.1.1 Approval Requirements

Approval is not required for local or regional presentations about the CleanUP-IPF, provided that the information presented has been released by the NHLBI and CleanUP-IPF Steering Committee (SC). Investigators may proceed with such presentations; and notification of the DCRI is not required.

Presentations about the CleanUP-IPF at national or international meetings, or invited papers about the CleanUP-IPF require approval from the CleanUP-IPF SC.

12.1.2 Abstract Proposal, Submission, and Approval Procedures

Abstracts that require new analysis of CleanUP-IPF data require approval of the Publication Committee prior to release of data to the investigator. The Abstract/Publication Proposal (Form PP) must be completed.

An abstract that uses CleanUP-IPF information already in the public domain need not be proposed before submitting a completed abstract to the Publication Committee for review; in this case, the abstract should be submitted in the format required by the meeting's program committee.

Content of the abstract/Form PP must be reviewed by the Principal Investigator of the center submitting the abstract/Form PP (if the abstract/Form PP includes investigators from more than one center, one investigator/center must be designated as responsible and the Principal Investigator of that center must review and sign the content of the abstract/Form PP).

The abstract/Form PP should be sent to DCRI for circulation to the Publication and Executive Committees.

The Publication Committee will determine if there is overlap between the abstract/Form PP and any other abstracts or publications that have been proposed or are in progress. If overlap exists, the investigator will be encouraged to collaborate on the existing project. The Publication Committee will vote on disposition of the abstract/Form PP. DCRI will provide each member of the Publication Committee with the abstract/Form PP and a ballot for voting, with a deadline for a response. A majority vote for approval by those Publication Committee members who send in their ballot is required for approval of an abstract/Form PP. Otherwise, the abstract/Form PP will be disapproved. Additionally, the Publication Committee will set priorities for DCRI with respect to multiple commissioned abstracts.

An abstract prepared in response to Publication Committee approval of an abstract proposal (Form PP) must itself be approved by the Publication Committee (that is, approval of an abstract proposal does not constitute approval of the resulting abstract; the abstract itself must also be approved).

An abstract may not be submitted if disapproved by the Publication Committee; if the abstract has already been submitted, it must be withdrawn. Unfavorable Publication Committee decisions can be appealed to the SC.

Author is not obligated to submit an abstract even if it has been approved.

Approval of an abstract does not equate to approval to develop a manuscript based on the abstract.

DCRI will provide the Publication Committee's decision in writing to the proposing investigator.

12.1.3 Data Analysis and Related Resources

If the abstract requires data analysis or related resources from DCRI, responsibility for data analysis and these resources should be specified and agreed upon, at the time of submission of the abstract proposal to DCRI. Because of resource limitations, the DCRI may not be able to respond to all requests as quickly as investigators would like.

Analysis of the primary and secondary outcomes manuscripts must be done by DCRI.

Investigator initiated abstract or presentation or local or regional presentation: unless otherwise specified and agreed upon, data analysis will be the responsibility of the proposing investigator. For an analysis to be performed outside the DCRI stats group, the manuscript PI needs to demonstrate that there is adequate resources to perform and document the analysis to be conducted, such as access to a statistician with clinical trial experience, a secure computing system, and a method to document and repeat an analysis. These factors should be reviewed by the head of the Publications Committee, DCRI statistician, and NIH representative.

Outcome data by treatment group may not be presented prior to publication of CleanUP-IPF primary trial results.

12.1.4 Authorship, Attribution, and Author Responsibilities

Name of presenter should be listed in abstract and in program.

For commissioned abstracts, the lead author is expected to make the presentation.

Abstracts and presentations relating to the main CleanUP-IPF trial, secondary outcomes, and sub-studies: authorship should be specified as "Name A, Name B, Name C, ...for the CleanUP-IPF Research Group."

Abstracts and presentations relating to ancillary studies: authorship will be "Name A, Name B, Name C...;" there should be acknowledgment of the CleanUP-IPF resources used by the ancillary study in the abstract or presentation.

Author must provide a copy of the abstract as submitted to the meeting's program committee to DCRI for the study archive.

12.2 Publications

12.2.1 Types of Papers

Mainline: dealing with the primary outcome (survival, exercise capacity), major hypotheses, or overall aspects of the trial (e.g. overall recruitment effort, population description). Analysis of the primary outcomes of the trial must be done by DCRI.

Secondary: dealing with a secondary outcome of the trial, sub-study, or an aspect of the trial

that is more “select” than “general”—this decision will be a judgment call and can be debated.

Ancillary: resulting from an CleanUP-IPF ancillary study

12.2.2 Applicable Policy

Mainline and secondary papers are subject to the policy that appears on the following pages.

Ancillary papers are subject to the policy that appears on the following pages with the following exceptions:

- Self-initiated ancillary papers—those that do not have to be proposed and approved before work commences on the paper once written, ancillary papers will go through the same review process prior to journal submission that mainline and secondary CleanUP-IPF papers have to go through.
- Will not necessarily have data analyses checked by DCRI.

12.2.3 Publications Committee Functions

The Publications Committee has two main functions:

1. Commission writing groups to prepare mainline or secondary papers on topics suitable for publication (editorial function).
2. Provide review of draft manuscripts (mainline, secondary, and ancillary) on behalf of the CleanUP-IPF SC (review function).

Editorial functions for mainline and secondary papers:

1. Solicit and identify topics suitable for mainline or secondary publications
2. Review and approve/disapprove publication proposals
3. Make recommendations to Executive Committee/Steering Committee regarding topics to be commissioned
4. Decide on authorship format for each commissioned paper
5. Nominate writing committee members along with proposing investigator
6. Provide written summaries of reviews to the proposing investigator and DCRI
7. Prioritize assignments for DCRI, persons, or groups with multiple assignments
8. Monitor progress on commissioned papers and report on progress as requested
9. Take corrective action if work on a paper is not progressing

Review function for mainline, secondary, and ancillary papers:

For each paper, appoint two research group members to provide a written internal review.

Internal review should ensure that the paper adheres to the following criteria:

- Accurately describes CleanUP-IPF procedures and data
- Is consistent with other CleanUP-IPF papers, or if inconsistent, gives an explanation
- Is not excessively redundant or overlapping with current or commissioned papers
- Makes use of appropriate expertise among the investigators

Provide a written summary and copies of the reviews to the author, and provide a copy of the

correspondence to DCRI.

Resolving disputes:

The Publications Committee will make recommendations to the CleanUP-IPF SC to resolve disputes over issues that may arise concerning authorship, manuscript content, and reviewers' comments.

If consensus is not reached by the Publications Committee, the matter will be referred to the CleanUP-IPF SC.

12.2.4 Authorship and Credits

Guidelines for mainline and secondary papers:

Proposing investigators may suggest an authorship format.

Authorship format will be decided for each commissioned paper individually by the Publications Committee.

Journal permitting, every paper will include the full credit roster, so long as the site has enrolled at least one patient into the trial.

Guidelines for ancillary papers:

Authorship format will be conventional.

Every ancillary paper must include acknowledgment that the effort results from an ancillary study of the CleanUP-IPF and that the CleanUP-IPF is supported by contracts from the NHLBI.

The CleanUP-IPF credit roster should not be included.

Authorship definitions:

Corporate: Masthead (indexed) author = "CleanUP-IPF Research Group"; membership of writing committee is nowhere specified in the published article

Modified corporate: Masthead (indexed) author = "CleanUP-IPF Research Group"; title page footnotes include a listing of the writing committee for the paper; the writing committee for the paper will determine the order of the named authors in the footnote

Modified conventional: Masthead (indexed) author = "Name A, Name B, Name C, etc. for the CleanUP-IPF Research Group"; the writing committee for the paper will determine the order of the named authors

Conventional: Masthead (indexed) author = "Name A, Name B, Name C"; the writing committee for the paper will determine the order of the named authors

12.2.5 Selecting Writing Committee Members for Mainline and Secondary Papers

Selecting writing committee members:

For mainline manuscripts, the Protocol Committee Co-Chairs will propose the Writing Committee members.

For secondary manuscripts, the proposing Principal Investigator will propose the Writing Committee members.

The SC will approve or disapprove the nominations. Considerations for selection of members are as follows:

- All members of the CleanUP-IPF should be considered
- Committees should include representation from as many centers as reasonable
- Expertise and interest of CleanUP-IPF members should be used to CleanUP-IPF advantage

Making modifications to writing committees:

The Publications Committee may recommend changes to a writing committee.

Changes could be to replace a member or disband a committee.

Changes to committees must be approved by the Steering Committee prior to enactment.

12.2.6 Initiating Procedures for Mainline and Secondary Papers

Papers are proposed by the CleanUP-IPF SC, Executive Committee, or Principal Investigators via submission of the Abstract/Publication Proposal (PP) form to DCRI; DCRI will forward the form to the Publications Committee with comments on the availability of any data requested.

Publications Committee will review the proposal for appropriateness and assess any overlap between it and other proposed or commissioned papers.

The Writing Committee will be established as described in this policy (see Section 3.6.). The CleanUP-IPF SC will approve or disapprove the proposed committee.

Publications Committee will communicate in writing with the proposing Investigator and Writing Committee Chair regarding approval or disapproval; a copy of the letter will be sent to DCRI.

Upon approval by CleanUP-IPF SC, the paper is considered commissioned.

Approval of an abstract proposal or abstract does not constitute approval of a paper. When an investigator wants to expand an abstract to a paper, another Abstract/Publication Proposal (PP) form must be submitted.

12.2.7 Responsibilities of Writing Committees

Writing Committee Chair is responsible for the following items:

- Providing input for composition of the Writing Committee
- Assigning tasks to Writing Committee members
- Submitting the manuscript draft to DCRI, Publications Committee and NHLBI, respectively, for their review at the appropriate time
- Determining order of named authors for footnote or masthead, depending on authorship format; the major criterion shall be the effort and contribution made by the members in preparation of the manuscript
- Choosing the journal, in conjunction with the SC Chair to which the manuscript will be submitted. The choice of journal must be approved by the SC.
- Corresponding with co-authors, communicating with DCRI and Publications Committee, responses to the NHLBI review, and correspondence with journal editors
- Distributing to DCRI copies of drafts circulated to groups outside the writing committee and correspondence relating to the internal review process and with journals
- Maintaining a local archive of drafts, correspondence, and supporting materials relating to generation of the manuscript; the writing committee chair can use his/her judgment regarding which materials to retain in this local archive
- Submitting to DCRI a complete, exact copy of the paper as submitted to the journal at the time of submission
- Send galleys to DCRI so that DCRI may complete its final check of the paper

Writing Committee members are responsible for the following items:

- Perform tasks assigned by the chair.
- Contribute substantively to manuscript preparation; a member may be dropped if no substantive contribution is made.
- Provide status reports on progress as requested by the Publications Committee.
- Maintain confidentiality of data.

If a writing committee member does not accomplish the tasks assigned to him/her and has not contributed to the publication, the writing committee chair can request that the Publications Committee removes that individual from the Writing Committee.

12.2.8 Review Guidelines for Mainline, Secondary, and Ancillary Manuscripts

Regardless of authorship format, the review process applies to CleanUP-IPF mainline, secondary, and ancillary papers.

Writing Committee decides when to initiate the review process for their manuscript; all types of reviews must be completed prior to journal submission.

Writing Committee is responsible for dealing with comments from reviewers.

Publications Committee Chair and DCRI will each determine at the end of their respective reviews if the revised manuscript should be re-reviewed by any reviewers prior to proceeding to the next step in the review process and must provide written instruction to the author regarding the re-review requirements.

Each review step must culminate in a written message to the Writing Committee Chair with copy to DCRI.

This is the minimal review process—additional reviews may be sought by the Writing Committee.

All reviews will have deadlines for response.

12.2.9 Review Procedures for Mainline Manuscripts

Steps in review process:

1. Review by DCRI is simultaneous with circulation to the SC and NHLBI for voluntary comment from members
2. Review by Publications Committee
3. Check of galleys by DCRI and corresponding author

First DCRI review:

This is the first review in the process.

All data analyses must be confirmed by DCRI (analysis of primary outcomes must be done by DCRI).

DCRI reviews manuscript for factual correctness of statements about CleanUP-IPF.

DCRI notifies the Writing Committee Chair in writing regarding their analyses and whether re-review is necessary before the paper is submitted to the Publications Committee; a copy of the review is sent to the chair of the Publications Committee and the NHLBI.

Steering Committee review:

This review occurs simultaneous with DCRI review.

Manuscripts received for the first DCRI review will be circulated to the SC for voluntary comment directly to the Writing Committee Chair.

A deadline for return of comments to the Writing Committee Chair will be specified; the understanding is that failure of a SC member to comment implies approval.

Internal Publications Committee review:

This review occurs subsequent to DCRI and SC review.

Internal review should ensure that papers adhere to the following:

- Accurately describe the CleanUP-IPF procedures and data
- Are consistent with each other, or if inconsistent, give an explanation
- Are not excessively redundant or overlapping with current or commissioned papers
- Make use of appropriate expertise among the investigators

The internal review should distinguish between helpful suggestions, which authors may accept or ignore and required revisions based on one of the rationales listed above.

Internal reviewers are appointed by the Publications Committee; deadlines will be set for return of reviews to the Publications Committee Chair.

Internal reviewers send their written reviews to the chair of the Publications Committee who will forward the reviews to the writing committee chair and will indicate to the author whether re-review by the Publications Committee is necessary prior to the second DCRI review; copies of the reviews are forwarded to DCRI and the NHLBI.

Second DCRI review:

All data analyses must be re-confirmed by DCRI.

DCRI reviews manuscript for factual correctness of statements about CleanUP-IPF.

CleanUP-IPF presentations and publications:

DCRI notifies the writing committee chair in writing regarding their analyses and whether re-review is necessary.

A copy of the review is sent to the NHLBI and chair of the Publications Committee.

NHLBI Project Officer notifies the Writing Committee Chair in writing regarding his/her review and sends a copy to the DCRI and PC Chair.

Check of galleys by DCRI and corresponding author:

So that DCRI can complete their check, the corresponding author is responsible for completing a proof of the galleys, as well as forwarding a copy of the galleys to DCRI.

DCRI will complete a second, independent proof of the galleys for conformance with the submitted paper and final verification of all data presented in the paper.

12.2.10 Sequential Steps for Mainline

- 1) Writing Committee decides when draft is ready for submission to a journal.

- 2) At that time, the paper will be sent to DCRI; DCRI will distribute the draft to the SC and NHLBI for voluntary comment, and then proceed with their review and verification of data analyses.
- 3) Written notice of the review will be sent to the writing committee chair and will indicate any need for DCRI.
- 4) Re-review prior to submission to the Publications Committee.
- 5) Writing Committee receives comments from DCRI; SC comments are on a voluntary basis and are sent direct to the writing committee chair.
- 6) Writing Committee revises draft in accordance with DCRI comments and SC as appropriate.
- 7) Writing committee resubmits paper to DCRI if required and DCRI notifies chair of results of the re-review and permission to send paper to Publications Committee.
- 8) Writing committee submits draft to Publications Committee.
- 9) Publications Committee chair selects two reviewers.
- 10) Writing committee receives comments from reviewers and revises draft as appropriate and re-submits paper to Publications Committee as appropriate.
- 11) When writing committee believes paper is ready for journal submission, paper is resubmitted to DCRI for the second DCRI review.
- 12) After written clearance writing committee may submit to journal; a copy of the submitted paper must also be sent to DCRI at the time of journal submission.
- 13) Upon receipt of galleys, author sends copy of galleys to DCRI so that DCRI can complete its review of the galleys (this is additional to proof of galleys by corresponding author).

13.0 LABORATORY AND BIOSPECIMEN SAMPLE POLICIES AND PROCEDURES

13.1 Laboratory Samples

13.1.1 Shipping of the Lab Supply Kits from Biorepository Laboratory and Tracking

The CleanUP-IPF biorepository laboratory will ship the initial package of laboratory supply kits to each site when the lab is notified by the NEMO that each individual site is ready to receive their green-light/site activation letter. In many cases, the lab kit package shipment will be shipped out on the same or next business day.

The CleanUP biorepository laboratory will provide each site a lab kit supply shipment. Within the package, sites will find instruction sheets for blood, buccal, and fecal samples collections as well as 5 individual Ziploc bags labeled for patient #1~#5 for the first shipment and an increment of 5 numbers afterwards per shipment. Within each Ziploc, you should find:

- a). One printed, self-adhesive label sheet for baseline and 12 month visits.
- b). Four SWUBE Applicators.
- c). Two pre-stamped, self-addressed cushioned yellow envelopes.
- d). Two PAXgene Blood DNA tubes.
- e). Three PAXgene Blood RNA tubes.

13.2. Biomarker/Biospecimen Samples Collection and Repository

Note: Upon patient's visit, be sure to read the instructions carefully before sample collections. All samples should be processed using standard procedures (BSL-2) for handling biological samples. All samples should be stored in tubes labeled with the date of processing/acquisition and the patient's CLEANUP-IPF identification number. Save the 12 month visit labels for future use.

13.2.1 Right and Left Cheeks Buccal Sample Collection and Shipping Instructions

Subjects will be subjected to two buccal and two fecal samples collection, respectively, for microbial ecology.

- 1) Thoroughly rinse out the subject's mouth twice with water. We recommend that subjects abstain from drinking coffee before tissue collection.
- 2) Carefully remove the individual wrapper of the SWUBE™ Applicator. Twists open the cap and remove the culture swabs. Do not touch the cotton swab and plastic shaft.
- 3) Insert the SWUBE™ Applicator into **right side** of the mouth between the inside of the cheek and the upper gum. Press firmly and twirl the SWUBE™ Applicator against the inside of the inner cheek for at least 30 seconds to collect cells, using an up and down motion from front to back and back to front. Use a stopwatch or the second hand of a watch/clock to time the collection. This sampling technique should collect buccal cells without drawing blood.
- 4) Place the SWUBE™ Applicator back into the original tube. Replace the cap.
- 5) Label the swab with subject number, the date, and right side of the patient's mouth was swabbed.
- 6) Insert the SWUBE™ Applicator into **left side** of the mouth between the inside of the cheek and the upper gum. Press firmly and twirl the SWUBE™ Applicator against the inside of the inner cheek for at least 30 seconds to collect cells, using an up and down motion from front to back and back to front. Use a stopwatch or the second hand of a watch/clock to time the collection. Take great caution not to touch the inside of your tongue, teeth, or lips. This sampling technique should collect buccal cells without drawing blood.
- 7) Place the SWUBE™ Applicator back into the original tube. Replace the cap.
- 8) Label the swab with subject number, the date, and left side of the patient's mouth was swabbed.
- 9) Place both SWUBE™ applicators in one of the yellow envelopes provided and drop it off in outgoing USPS mailbox ASAP.
- 10) Send an email to Shwu-Fan Ma, Director of the CleanUP Biorepository Laboratory at: SM7WN@hscmail.mcc.virginia.edu to inform about the shipment. The Biorepository Laboratory Director will reply to the email once the samples were received. Keep in mind that the biorepository lab will not process these samples for microbial ecology study immediately. The date of sample process is yet to be determined.

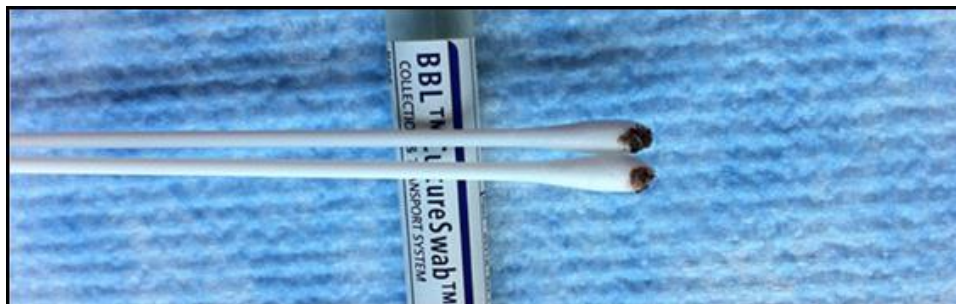
All buccal samples should be shipped via United States Postal Service, at room temperature, to the following address:

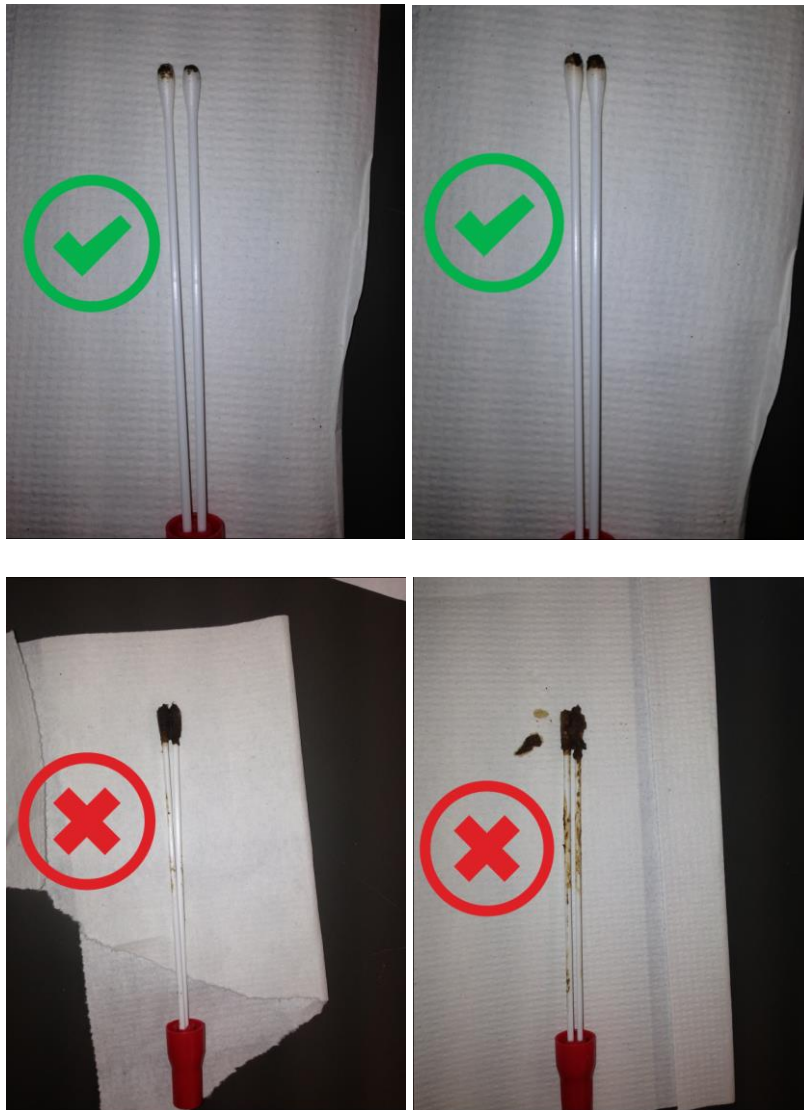
Biorepository Core Laboratory
Attn: Shwu-Fan Ma, PhD
c/c: Marie Burdick
University of Virginia, Division of Pulmonary & Critical Care Medicine
P.O. Box 800546
Charlottesville, VA 22908
Tel: (434) 924-0350
Email: SM7WN@hscmail.mcc.virginia.edu

13.2.2 Fecal Sample Collection and Shipping Instructions

- 1) Carefully remove the individual wrapper of the SWUBE™ Applicator. Twists open the cap and remove the culture swab. Do not touch the cotton swab and plastic shaft.
- 2) Rub both cotton tips on a fecal specimen (ideally, a used piece of toilet paper) to collect a small amount of biomass, saturating half the swab at maximum.

Note: More is not better! The ideal amount of biomass collected is shown in the figures below for two reasons. First, the amount of material could bias the result of your sample (e.g. mold growth might contaminate the sample). Second, excess material cannot be handled by our processing pipeline.





- 3) Place the SWUBE™ Applicator back into the original tube. Replace the cap.
- 4) Label the swab with the date of the patient's feces was swabbed.
Place the applicators in one of the yellow envelopes provided and drop it off in outgoing USPS mailbox ASAP.
- 5) Send an email to Shwu-Fan Ma, Director of the CleanUP Biorepository Laboratory at: SM7WN@hscmail.mcc.virginia.edu to inform about the shipment. The Biorepository Laboratory Director will reply to the email once the samples were received. Keep in mind that the biorepository lab will not process these samples for microbial ecology study immediately. The date of sample process is yet to be determined.

All fecal samples should be shipped via United States Postal Service, at room temperature, to

the following address:

Biorepository Core Laboratory
Attn: Shwu-Fan Ma, PhD
c/c: Marie Burdick
University of Virginia, Division of Pulmonary & Critical Care Medicine
P.O. Box 800546
Charlottesville, VA 22908
Tel: (434) 924-0350
Email: SM7WN@hscmail.mcc.virginia.edu

Alternative Fecal Samples Collection

We recognize that some participants have chronic constipation. In these instances, what we recommend is the “catch and release” method, using 2-4 paper towels (enough to not get any on you, but to also avoid clogging the toilet). If the specimen is not soft, please just rub both sides of the cotton swabs on it to get a light smear. And of course, make sure to wash your hands afterwards.

- 1) Place the SWUBE™ Applicator back into the original tube. Replace the cap.
- 2) Label the swab with the date of the patient’s feces was swabbed.
- 3) Place the applicators in one of the yellow envelopes provided and drop it off in outgoing USPS mailbox ASAP.
- 4) Send an email to Shwu-Fan Ma, Director of the CleanUP Biorepository Laboratory at: SM7WN@hscmail.mcc.virginia.edu to inform about the shipment. The Biorepository Laboratory Director will reply to the email once the samples were received. Keep in mind that the biorepository lab will not process these samples for microbial ecology study immediately. The date of sample process is yet to be determined.

All fecal samples should be shipped via United States Postal Service, at room temperature, to the following address:

Biorepository Core Laboratory
Attn: Shwu-Fan Ma, PhD
c/c: Marie Burdick
University of Virginia, Division of Pulmonary & Critical Care Medicine
P.O. Box 800546
Charlottesville, VA 22908
Tel: (434) 924-0350
Email: SM7WN@hscmail.mcc.virginia.edu

Additionally, subjects are permitted to take the fecal sample collection kits home if unable to provide a sample on-site. Please be sure to send these subjects home with a copy of the Fecal Sample Collection Instructions document, located on the PTC web portal.

13.2.3 Blood Sample Collection and Storage Instructions

For each subject, a total of 24.5 mL of blood will be collected into five tubes using the standard venipuncture technique. Ensure that the PAXgene Blood RNA and DNA Tubes (A) are at room temperature (18°C-25°C) prior to use and are properly labeled with patient identification and date of collection. If the PAXgene Tubes are the only tubes to be drawn, a small amount of blood should be drawn into a “Discard Tube” prior to drawing blood into the PAXgene tubes. Otherwise, the PAXgene Tubes should be the last tube drawn in the phlebotomy.

- Hold the PAXgene Blood RNA/DNA Tubes vertically, below the blood donor’s arm, during blood collection. Keep in mind that you should wait until the blood has stopped flow into the tube before removing the tube from the holder to ensure maximum amount of blood per tube. For PAXgene™ Blood RNA Tubes, you will draw 2.5 ml blood to each tube for a total of three tubes. For PAXgene™ Blood DNA Tubes, you will draw 8.5 ml blood to each tube for a total of two tubes.
- Invert PAXgene™ tubes 8-10 times immediately after blood drawn.
- Put tubes in storage boxes labeled “CleanUP-IPF” and store them at -20°C for 24 hours then transfer the tubes to -80°C.

13.2.4 PAXgene Blood RNA/DNA Tubes in Dry Ice Shipping Instructions

PAXgene Blood RNA/DNA Tubes will be consolidated and shipped to the biorepository laboratory in batches in dry ice.

Sites will batch ship blood samples to the CleanUP-IPF biorepository laboratory after a total of twenty (20) blood sample tubes (two full shipper boxes) have been collected. Once two shipper boxes are full, the site will notify the CleanUP biorepository lab that they have blood samples ready to ship to the lab. The biorepository lab will give the site an acknowledgement/authorization to ship the samples to the lab, and the laboratory’s FedEx account will be provided.

In preparation for shipping, the Site Coordinator should review the Specimen Log for each freezer box being shipped and confirm that the vials listed in the Specimen Log are in fact contained in the freezer box. The shipping address is:

Biorepository Core Laboratory
Attn: Shwu-Fan Ma, PhD
c/c: Pei-Chi Hou, Professor of Medicine
University of Virginia, Dept. of Medicine

Division of Pulmonary & Critical Care Medicine
1340 Jefferson Park Ave., Pinn Hall, RM#2232
Charlottesville, VA 22908
Tel: (434) 924-0350
Email: SM7WN@hscmail.mcc.virginia.edu

Note: Frozen PAXgene™ Blood Tubes are subject to breakage upon impact. To reduce the risk of breakage during shipment, frozen tubes should be treated in the same manner as glass tubes.

Contact FedEx to schedule/confirm pick-up service.

1. Check shipment boxes for the following:
 - a. To Label (To <STUDY> Repository)
 - b. From Label (From your site)
 - c. 24 Hour Emergency Contact Label
 - d. Responsible Person Label
 - e. Class 9 Diamond Label with Dry Ice Un 1845 Label and space to add weight and shippers address.
 - f. UN3373 Biological Substance Category B Label
2. Place excess amount of dry ice around sample storage boxes and Styrofoam container).



3. Add additional dry ice to bring total amount to the same level as the top of the sample storage boxes. Note that the total amount of dry ice will be ~16lbs or 7.3kgs



4. Place the Styrofoam lid on top the container and tape the Styrofoam lid.
5. Place packing slip in the cardboard box and seal it.
6. Send an email to Shwu-Fan Ma, Director of the CleanUP Biorepository Laboratory at: SM7WN@hscmail.mcc.virginia.edu to inform about the shipment. The Biorepository Laboratory Director will reply to the email once the samples were received. Keep in mind that the biorepository lab will not process these samples for microbial ecology study immediately. The date of sample process is yet to be determined.



7. Review the FedEx Airbill provided by <STUDY> and provide any missing information:
 - a. Section 2 – The “Internal Billing Reference Section” must have the following information “138, Biological Substance Category B”
 - b. Section 4a - Check the “FedEx Priority Overnight” box
 - c. Section 5 - Check the “other” box
 - d. Section 6 - Check the box that says, “Yes Shipper’s Declaration not required”. Check the “Dry Ice box” and write “1” in the first blank line and the “kg” of dry ice used on the second line; i.e., 1 x 7.3 kg
 - e. Section 7 - Check Recipient.
8. Fill in the Dry Ice Label on box with the total amount of dry ice used.
9. Include study specific instructions regarding specimen tracking system data entry here.

13.3 Potassium and Kidney Function Samples and Monitoring (**Note: For participants randomized to antimicrobial therapy **ONLY**)

Recent clinical practice has shown a potential link between antimicrobial therapy and an elevated risk for developing hyperkalemia. Subjects participating in the trial who are randomized to antimicrobial therapy will be subjected to additional renal function testing, as well as potassium lab values from scheduled blood draws, in order to closely monitor for the onset of hyperkalemia.

The following procedures will be performed prior to randomization, if results are not available from recent clinically indicated testing:

- Blood draw for the following lab tests:
 - Chemistry panel and liver function tests– defined as minimum of sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), and creatinine, total bilirubin, direct bilirubin, alkaline phosphatase (ALP), alanine transaminase (ALT), and aspartate aminotransferase (AST)
 - Complete Blood Count (CBC)

If a subject does not meet the eligibility criteria due to a condition that subsequently resolves (e.g., infection or renal insufficiency), they may be considered for enrollment once the condition resolves if they meet the all eligibility criteria at the time of randomization.

Subjects randomized to co-trimoxazole therapy will have blood drawn at the One (1) week visit, to evaluate their tolerance of co-trimoxazole therapy.

Additionally, subjects randomized to antimicrobial therapy will have blood drawn at each of the following study visits to evaluate their tolerance of their assigned antimicrobial therapy:

- Three (3) month visit
- Six (6) month visit
- Twelve (12) month visit
- Twenty-four (24) month visit

If a subject randomized to the antimicrobial strategy group develops intolerance to co-trimoxazole, the dosage can be decreased to one double strength 160mg trimethoprim/800mg sulfamethoxazole (co-trimoxazole) three times weekly plus folic acid 5mg daily. If intolerance continues with co-trimoxazole, then the antimicrobial agent can be changed to doxycycline.

14.0 RADIOLOGY & CT SCANS

14.1 CT Scans

For CleanUP-IPF, patients will have a CT scan as part of their clinical diagnosis, but this is not

required within the CleanUP-IPF protocol. All subjects should have a CT scan that will be used at baseline for a diagnosis confirmation, but the format and timing will vary, since this procedure is not included within the screening and/or baseline procedures listed in the CleanUP-IPF protocol.

15.0 CLINICAL SUPPLIES AND MATERIALS

NEMO contracts with various vendors for the purchase of supplies provided to the sites. The items are packaged and shipped by NEMO directly to the clinical sites prior to start-up. This process is also summarized in the “Pharmacy, Drug, and Study Materials Management Summary” document produced by the NEMO.

16.0 SITE PAYMENTS

A quarterly data export from the eCOS EDC database will list all subject visits that have been updated as completed within EDC. If there has been data entered for any visit and all applicable eCRF pages are completed, the visit will be listed as completed. This data export will be sent over to the NEMO, for their reconciliation of visits already having been paid to the site versus new visits being completed. The NEMO will then total up the current amount to be paid to each site and process the payments accordingly.

Capitation payment data will represent activity occurring in specific timeframes:

- Quarter 1: January 1st — through -- March 31st
- Quarter 2: April 1st – through -- June 30th
- Quarter 3: July 1st – through -- September 30th
- Quarter 4: October 1st – through -- December 31st

The following table details the Capitation Payment Criteria for the CleanUP-IPF study:

TASK	AMOUNT	CRITERIA
Randomization Visit (V1) 11V01T01	\$3,400	All forms to support eligibility Entered and Query Cleaned All other data forms Entered/Query Cleaned All Participant Questionnaires Entered and Query Cleaned Spirometry form Entered and Query Cleaned
Randomization Renal Function Panel, if required (V1) 11V01T02	\$50	Form Entered and Query Cleaned
Week 1 Follow-up Visit (V1A) **For subjects randomized to co-trimoxazole ONLY**	\$75	All data forms Entered and Query Cleaned
Month 1 Follow-up Call (V2) 11V02T01	\$50	All data forms Entered and Query Cleaned
Month 3 Follow-up Visit (V2A) *For subjects randomized to antimicrobial therapy ONLY*	\$75	All data forms Entered and Query Cleaned
Month 6 Follow-up Visit (V2B) *For subjects randomized to antimicrobial therapy ONLY*	\$75	All data forms Entered and Query Cleaned
Month 6 Follow-up Call (V3) 11V03T01	\$50	All data forms Entered and Query Cleaned
Month 12 Follow-up Visit (V4) 11V04T01	\$250	All data forms Entered and Query Cleaned All Participant Questionnaires Entered and Query Cleaned
Month 12 Spirometry/Pulmonary Function Test (V4) 11V04T02	\$300	Spirometry form Entered and Query Cleaned
Month 12 Renal Function Panel, if required (V4) 11V04T03	\$50	Form Entered and Query Cleaned
Month 18 Follow-up Call (V5) 11V05T01	\$50	All data forms Entered and Query Cleaned
Month 24 Follow-up Visit (V6) 11V06T01	\$250	All data forms Entered and Query Cleaned All Participant Questionnaires Entered and Query Cleaned
Month 24 Renal Function Panel, if required (V6) 11V06T02	\$50	Form Entered and Query Cleaned
Month 24 Spirometry/Pulmonary Function Test (V6) 11V06T03	\$300	Spirometry form Entered and Query Cleaned

Month 30 Follow-up Call (V7) 11V07T01	\$50	All data forms Entered and Query Cleaned
Month 36 Follow-up Call (V8) 11V08T01	\$50	All data forms Entered and Query Cleaned
TOTAL	\$4,750	
TOTAL with Co-Trimoxazole Labs, Antimicrobial Labs, and Renal Function Panels (if required)	\$5,125	

All checks will be mailed with a listing of subjects and visits that are included within the enclosed payment. Due to all the steps involved, expect to receive payment within six weeks of the end of each quarter.

Inquiries concerning the content in the invoice should be directed to the NEMO Financial Administrator.

The University of Pittsburgh utilizes a paperless payment system (PantherExpress) that provides an efficient, effective and streamlined process of making and tracking payments. All payments are keyed in by the Financial Administrator, and payments are issued by the Payment Processing Department. Each clinical site is issued an internal purchase order number based on project after receipt of the executed subaward agreement. The budget cap is used when setting up the purchase order, and payments are automatically deducted from the cap. No payments are allowed once the cap is reached, and modification of the cap requires an executed subaward amendment.

17.0 SITE VISITS/SITE MANAGEMENT AND MONITORING

The NEMO shall be responsible for all activities associated with site visits, site management, and site monitoring. No site visits will be conducted or completed by the CleanUP-IPF PLG and/or DCRI. Neither the CleanUP-IPF PLG nor DCRI will source documents from sites against data that is entered into the eCOS EDC database (site monitoring). The CleanUP-IPF PLG and DCRI will review subject data on a very broad term via monthly and quarterly metrics reports that will be generated for reporting to the NHLBI, NEMO, and/or DSMB.

The NEMO will be reviewing data query reports monthly and will follow up with sites accordingly, in an effort to resolve and close data queries as quickly as possible.

The NEMO will be responsible for all site communications except correspondence regarding subject safety and medical monitoring issues. As DCRI is tasked with safety surveillance and medical monitoring for the CleanUP-IPF trial, DCRI will be responsible for site correspondence regarding these issues.

17.1 Site Data Metrics and On-Site Visit Triggers

The CleanUP-IPF PLG will be reviewing monthly metrics reports including site enrollment

reports, EDC data metrics reports, safety reports, etc. Specific metrics will be deemed as those in which parameters will be put into place to trigger a potential on-site visit by the NEMO and/or NHLBI representative.

Site metrics will document activity occurring in specific timeframes:

Quarter 1: January 1st – through -- March 31st

Quarter 2: April 1st – through -- June 30th

Quarter 3: July 1st – through -- September 30th

Quarter 4: October 1st – through -- December 31st

17.2 Site Trainings and Materials

CleanUP-IPF clinical sites will be trained (via online WebEx training sessions through the PTC website) in the following areas:

- Good Clinical Practice (GCP) overview
- Inclusion / exclusions
- Protocol activities
- Telephone contact methodology
- SAE reporting expectations
- Blood draw requirements
- Sample processing, storage, and shipping
- Electronic data capture
- Accessing the EDC
- Data entry requirements and scheduling expectations
- Query resolution procedures
- Uploading documentation for outcome event classification

18.0 REPORTS AND DSMB

18.1 DSMB Meeting Reports

18.1.1 Open Book

- Design summary
- Trial status including minutes and recommendations, responses to those recommendations, new challenges and how they are being handled
- Consort chart
- Recruitment (over time and by clinical site). Barriers to recruitment and strategies to address recruitment shortfalls are discussed
- Baseline characteristics of randomized patients (not separated by intervention group)
- Withdrawal of trial participants

- Study visit completion and Data completeness (overall and by clinical site)
- Protocol deviations
- Serious adverse events (not separated by intervention group)

18.1.2 Closed Book

- Baseline characteristics of randomized patients (stratified by intervention group)
- Primary and secondary outcome measures (NOT stratified by intervention group)
- Serious Adverse events (stratified by intervention group)
- Deaths (NOT stratified by intervention group)
- Respiratory hospitalizations (NOT stratified by intervention group)

18.1.3 Interim Monitoring (as appropriate according to the design of the trial; not included at every meeting)

- Statistical comparison of primary outcome measures by assigned intervention group
- Statistical comparison of designated safety outcome measures by assigned intervention group

18.2 Ad-hoc Meetings

In the case of expedited reporting the PLG prepares the DSMB report and provides it to the NEMO within the prescribed time for the type of event. The NEMO and NHLBI then distribute the event report to the DSMB members for review and voting.

- Deaths (NOT stratified by intervention group)
- Respiratory hospitalizations (NOT stratified by intervention group)

19.0 GENERAL CONSIDERATIONS

19.1 Questionnaire Administration

Questionnaires and subject surveys will be collected as part of the study. These instruments may be collected by participant interview with coordinator, or by participant self-completion. The information in this section is meant to provide general guidance in administration of questionnaire and survey assessments.

19.1.1 Testing Environment for Administering Questionnaires

19.1.1.1 In-Person Visits

For any in-person participant contact, the researcher will provide the participant with a quiet, private area to administer questionnaires (e.g., exam room, office, etc.). Family members/friends will be asked to wait in another area; do not allow family members/friends to answer the questions for the participant or give their opinion of the questions or responses.

19.1.1.2 Phone Visits

For any participant contact via telephone, the researcher will work with the participant to choose an appropriate time in which the participant can be contacted to answer questions. This should be a time when the participant is not rushed to leave the home or distracted by family/friends who may be visiting.

19.1.2 Establishing Rapport

Establishing rapport with a participant is important to elicit cooperation with study procedures. The interaction between the coordinator and participant could affect the participant's performance and responses. Establishing rapport with the participant is essential so that they are at ease and are able to give their best performance during testing. A participant who is anxious or uncomfortable will be too distracted to perform adequately.

There are some basics of establishing rapport:

- Try to establish rapport to put the participant at ease before beginning. Engage in a bit of casual conversation before testing
- Always be pleasant and patient
- Check to make sure the participant is comfortable before testing (e.g., warm enough, need to use restroom, etc.). For phone call contact, confirm with the participant that this is a good time to complete required tasks
- Be sure to give the participant a good idea of exactly what will happen during the visit/phone call before beginning
- Do not rush any of the aspects of your interaction with the participant
- Allow participants sufficient time to respond and to ask questions
- Keep in mind that each participant's personality will be different and some will respond better to you than others. Adjust your interaction with them accordingly. For example, keep a slower pace for those who require it, and move more quickly for those who prefer that kind of interaction

- For in-person contact, be readily available and in close proximity to the participant to quickly assist when necessary, without hovering
- Always thank the participant at the end of the session. Say something like, “I want to thank you for your participation today. I really appreciate your effort, attention, time (whatever is appropriate). It was a pleasure working with you”

19.1.3 General Questionnaire Guidelines

There are established guidelines for questionnaire administration, which are as follows:

- Administer all tests according to the directions on the forms
- Do not rephrase items when presenting instructions, questions, or responses to the participant
- Under ordinary circumstances, you should not tell the participant whether a specific response is correct or incorrect. If s/he asks, say something like “You’re doing fine. Let’s try this one.” If s/he insists, simply reply “I’m really not allowed to say”
- Emphasize that there are no right or wrong answers and responses should be the subjective view of the participant and not what others may think is most accurate
- Use good judgment and common sense
- Be prepared to make accommodations for auditory or other deficits. In case of hearing impairments, be sure to look at the participant when speaking, speak in lower tones, and do not speak too quickly
- Be flexible, but try to adhere to standardized test administration without being rude. For example, if a participant begins to tell an involved story, say something like, “I don’t want to interrupt, but we really need to move along with the testing – do you mind finishing that story when we’re all through?”
- On participant-completed questionnaires, it is very important to check the questionnaire to make sure a response has been given to every question. If they have missed an item, return the questionnaire to the participant for completion before they leave
- Document any assistance provided to the subject in completing questionnaires (e.g., coordinator read questions and responses to participant, etc.)
- Allow for sufficient time to complete questionnaires. When possible, plan to administer questionnaires at a time when participant will not be rushed to get to another test, perhaps at the end of a visit.

19.2 Pulmonary Function Tests (PFTs)

19.2.1 General Considerations

General information related to this section is consistent with the ATS/ERS Statement: General considerations for lung function testing.

19.2.1.1 Environmental Conditions

Ambient environmental conditions must include documentation of barometric pressure, temperature and relative humidity of the pulmonary laboratory where the equipment is located. These conditions must be measured accurately and controlled in a comfortable range

(temperature $>17^{\circ}$ and $<25^{\circ}\text{C}$ and relative humidity maintained in the range of 20-50%). If the temperature changes $\pm \geq 2^{\circ}\text{C}$ following calibration a repeat calibration check is required.

19.2.1.2 Basic Subject Demographics

Height, weight, gender, race, and age values are recorded at the screening visit. Date of birth should be entered rather than age. Height recorded at screening visit will be used for calculation of predicted value on subsequent visits. Protocols that perform plethysmography, the subject's weight will be measured at each visit and the subject's demographics will be updated on the pulmonary function software to reflect the subject's current weight.

Height must be measured with shoes removed. Using an accurate device (stadiometer preferred) have the subject place his/her heels and feet together, with back straight stand as tall as possible with eyes straight ahead to measure height, preferably in centimeters (nearest 0.1 cm), or in inches (nearest 1/4 inch). Weight must be measured at each visit in either pounds (nearest 1 pound) or kilogram (nearest ½ kilogram).

19.2.1.3 Subject Preparation and Communication

The subject should eat a light meal 2-4 hours prior to testing. Avoid alcoholic beverages within 4 hours and avoid caffeine-containing food and beverages within 8 hours of testing. The subject should wear clothing that will not restrict chest or abdominal expansion. Subjects should leave dentures in place and remove them only if they are loose and interfere with acceptable testing. Technicians and any staff conducting study tests, unless otherwise designated, must have no knowledge of the assignment of treatment or placebo group. Technicians must also avoid commenting or discussing the clinical status, positive or negative, of study subjects during their study visits. Technicians should avoid discussion of results or outcome information to the subject (or family member/friend). Technicians should not have test results from previous visits immediately available for their or subject viewing at the time of any subsequent visit.

19.2.1.4 Contraindications for PFT

Pulmonary function testing is contraindicated in subjects within 1 month following a myocardial infarction, recent abdominal or thoracic surgery, recent brain, ear, eye or ENT surgery, pneumothorax, ascending aorta aneurysm, hemoptysis, pulmonary embolism, acute diarrhea, angina, severe hypertension (systolic > 200 mmHg or diastolic > 120 mmHg, oral or facial pain exacerbated by a mouthpiece, stress incontinence and dementia or confused state. The subject must be cleared by the PI prior to participant in study specific procedures following any illness or medical procedure listed above.

19.2.1.5 PFT Data Transfer Procedures

Within PLGs that do not use the automated DataStream transfer process (e.g. CleanUP-IPF), digital source data will not be directly transferred to NEMO or the PLGs given the potential wide variation in data formatting across different equipment. PFT data worksheets and source documents will be transferred directly to the DCRI. Only the source documents addressing the

QA program protocol (section 1.7) will be sent directly to the NEMO from the sites by scanning the documents and uploading a PDF file of trial data and graphics via the NEMO website. The NEMO QA analyst will communicate via the NEMO website by uploading the corresponding documents related to all QA program matters and the certification process. The technicians will be automatically notified of these uploads. The sender must ensure the anonymity of the subject by making identifiable information unreadable.

19.3 Spirometry

19.3.1 Forced Spirometry Test Considerations

Spirometry test technique is referenced to the ATS/ERS Statement on Spirometry². Ensure that ≥ 4 hours has elapsed since the subject's last use of albuterol or salbutamol. Documentation of time of last maintenance bronchodilator should be recorded. Testing will be performed with the subject sitting upright, with the head slightly elevated and with nose clips on. The subject should maintain a head up, erect posture throughout the maneuver. Technical staff should demonstrate correct test technique. All spirometry must be performed using a "closed circuit" technique. The performance of a maximal inspiratory effort in addition to the standard maximal expiratory effort is to be performed at the discretion of study protocol.

Monitor subjects for distress, dizziness, syncope, air leak, tongue obstruction, cough, biting down on the mouthpiece and airway noises which may suggest oral or upper airway obstruction. Subjects with untoward symptoms should cease continued effort. Technicians should assess the cause of symptoms and correct subject test technique, if possible, and retest.

Subjects with a history of syncope during the FVC maneuver may achieve usable FVC efforts by using less than maximal force during the later phase of expiration although this modified technique must be entered in the technician test comments.

19.3.2 Forced Spirometry Test Considerations (3 Distinct Phases)

Maximal inspiration - Consists of a rapid and complete inspiration and should begin from a resting end expiratory level.

At full inspiration, with a breath hold of no greater than 1 second the subject should "blast" their air out. Exhalation should begin without hesitation and produce maximal airflow.

Continued complete exhalation to the end of test - Encourage subject throughout exhalation to expel as much air as possible.

A short rest of 30-60 seconds typically allows adequate recovery between testing maneuvers although the rest interval is indeterminate and the subject should be fully recovered prior to retesting.

19.3.3 Forced Spirometry Test Acceptability

The PFT technician should view the flow-volume loop and the volume-time tracing to assess test acceptability.

FVC (within-maneuver) test acceptability criteria:

- Spirogram is free of artifacts
- Satisfactory start of test
- Satisfactory end of test: Achieving an expiratory plateau where the volume-time curve shows no change (25 ml/sec for ≥ 1 second). A forced expiratory time of 15 seconds is recognized to be of sufficient duration in subjects with severe obstructive disease and “multiple prolonged exhalations are seldom justified and may cause light headedness, syncope, undue fatigue and unnecessary discomfort”. End of test criteria may be further satisfied in this patient population when, in the view of the technologist, that “the subject cannot or should not continue further exhalation”.
- No cough in the first second
- No glottis closure or valsalva maneuver which terminates expiration
- No early termination or cut-off
- No evidence of submaximal effort
- No evidence of leaking
- No hesitation or leak at start of test (extrapolated volume must be less than 150mL or 5% of FVC, whichever is larger)
- Satisfactory duration of effort (minimum 6 seconds)

19.3.4 Forced Spirometry (between-maneuver) Test Acceptability Criteria

Forced Spirometry testing must produce at least three acceptable spirograms with:

- 2 largest values of FVC must be within 0.150 L of each other. If FVC is <1.0 liter the 2 largest values of FVC and FEV₁ must be within 0.100 L of each other. If repeatability criteria are met for both FVC and FEV₁ the test session is over
- If repeatability criteria are not met for both FVC and FEV₁, continue testing until both criteria are met or a total of 8 tests have been performed. Discontinue testing if subject cannot or should not continue and notify study supervisor, coordinator or PI as appropriate.

19.3.5 Forced Spirometry Reporting Data

- Best (highest) FVC* and % predicted FVC
- Best (highest) FEV₁* and % predicted FEV₁

*Highest value can come from any acceptable trial.

(Note: these % predicted values will be necessary in real time to allow decisions regarding eligibility, however they will be calculated independently within the database from the raw values).

19.3.6 Assessing Bronchodilator Reversibility and Eligibility

Calculate FEV₁ reversibility according to the following formula:

- Post **BD percent (%)** change = (Best FEV₁ Post minus Best FEV₁ Pre) / Best FEV₁ Pre * 100

- Post **BD volume (ml)** change = Best FEV₁ Post BD (mL) minus Best FEV₁ Pre BD (mL)

Calculate FVC reversibility as specified according to:

- Post BD volume (ml) change = Best FVC Post BD (L) minus Best FVC Pre BD (L).

19.3.7 Slow Vital Capacity (SVC)

SVC testing will be performed following ATS/ERS Spirometry Standards². SVC measures the complete volume of air from maximal TLC to maximal RV. SVC technique varies from FVC in that effort is not maximal other than when the test approaches TLC and RV. Two standard techniques are recognized; 1) as IVC (Inspiratory Vital Capacity) and 2) as EVC (Expiratory Vital Capacity). Considerations for SVC testing are similar to FVC testing although the untoward effects of the FVC test tend to be lessened due to overall effort.

The preferred PFT study technique for slow Vital Capacity will utilize method 1. This technique allows for measurement of both VC and IC using a single test maneuver.

19.3.7.1 SVC (using IVC) Test Procedure

A slow vital capacity maneuver will be performed utilizing the EVC technique. This technique provides test results for VC and for IC as required for a NEMO trial.

Performing the SVC (EVC) test technique includes 4 phases as follows:

- Establish a stable tidal breathing pattern for several breaths. It is important that a stable resting end-expiratory level be determined (FRC level).
- Perform an expiratory maneuver to residual volume
- Perform a full inspiration to total lung capacity
- Perform an expiratory maneuver back to baseline (FRC level)

PFT technicians should:

- Demonstrate the rate of flow for both the IVC maneuver
- Provide vigorous coaching during the expiratory maneuver (step 2) to achieve plateau and to reach TLC (step 3). The rest interval between trials should be approximately 1 minute, but no specific rest interval is specified and the subject should have fully recovered from the last test before continuing.

19.3.7.2 SVC (IVC) Test Acceptability

The IVC maneuver graph should be inspected for acceptability. Acceptability criteria (applied to each maneuver): end of test criteria met (change in volume <0.025 L over 1 s) and no cough, glottic closure, leaks at the mouth or obstruction of mouthpiece. Three acceptable maneuvers out of up to a maximum of 4 attempts will be expected².

19.4 DLco

The 2005 ATS/ERS Task Force Statement on standardization⁴ of this test will serve as the technical reference for DLco measurement.

DLco(SB) is a pulmonary laboratory test technique that involves measuring the uptake of CO from the lung over a breath-holding period and is expressed as the amount of CO uptake per minute per driving pressure of CO.

$$DLco = \text{mL CO (STPD)} / \text{minute/mmHg}$$

19.4.1 DLco Test Conditions

DLco testing will always be performed Post BD or per protocol. Supplemental oxygen will be discontinued for a minimum of 10 minutes prior to DLco testing. The subject should avoid any unnecessary movement and avoid active conversation during this wait time. Monitor pulse oximetry as indicated. If the subject experiences inordinate dyspnea notify the study coordinator and PI. Re-administer supplemental oxygen as indicated for subject safety.

Anatomic deadspace should be estimated according to the following equation⁴:

$$VD = 2.2\text{mL} \times \text{kg body weight. (For BMI} \leq 30)$$

or

$$VD = 24 \times \text{height (squared)} / 4545 \text{ where height is measured in cm, (BMI} > 30)$$

If the subject's VC is ≥ 2.00 liters the washout volume is set at 0.75 liters and if the VC is < 2.00 liters the washout volume is set to 0.50 liters. Post-test adjustment of washout and sample volume may be possible with instrumentation that allows continuous display of exhaled gas concentrations. Breath-hold time should be calculated by the technique of Jones and Meade. No adjustment will be made to DLco results for hemoglobin concentration and CO back pressure. (Hgb adjustment can be made through the coordinating center data base when Hgb is available using the Cotes equation¹²) Adjustment for altitude should be made according to the following formula⁴:

$$DLco \text{ predicted for altitude} = DLco \text{ predicted} / (1.0 + 0.0031(P_{iO_2} \text{ minus } 150))$$

19.4.2 DLco Test Procedure

Following proper set-up and calibration of DLco test instrumentation the subject should attach to the mouthpiece and place noseclips. After one to five breaths the subject is instructed to exhale completely (to RV) at an easy pace. Subjects should exhale to RV in 6 seconds but should not exceed 10 seconds. Inspiration of test gas should be rapid and should be complete to TLC in < 4 seconds. The subject then breath-holds for 9 to 11 seconds and attempts to maintain a near atmospheric pressure (neither positive nor negative pressure) for the entire breath hold time. Following breath holding instruct the subject to exhale rapidly without "blasting". Exhalation should be accomplished in < 3 seconds which is readily done in subjects with restrictive disease although this may be difficult to achieve with obstructed subjects. Exhalation time should be recorded. Wait at least 4 minutes between trials. Obtain a minimum of two acceptable trials, but attempt no more than five trials.

19.4.3 DLco Test Acceptability and Repeatability Criteria

Inspiratory time	90% complete at < 4 seconds
Inspiratory volume	>85% of maximum of SVC or FVC
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
Expiratory time	Expiration in < 4 s (and sample collection time <3 s), with appropriate clearance of VD and proper sampling/analysis of alveolar gas
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
Repeatability	Minimum 2 trials agreeing within 10% or 3.0 mlCO- STPD/min/mmHg of mean, maximum 5 session, > 4 minutes between trials

19.4.4 DLco Report Data

- DLco (uncorrected): The mean of at least two acceptable, repeatable test results is reported
- DLco % predicted: Utilize Crapo predicted set for reference values⁷
- Alveolar Volume (V_A) in Liters
- Inspired Volume (V_I) in Liters. Report each value of V_I used to determine DLco

19.5 Ancillary Studies

An ancillary study for a given PLG is defined as any study where data outside the original scope of the project is collected and additional resources are required to collect the data. Each PLG is to develop their own ancillary study application and review process which is subject to approval by the PTC Operations Committee prior to implementation. Details on this process can be found in the Manual of Operation for each PLG.

The review of an ancillary study application by a PLG is to include feedback from the NEMO on two aspects:

- The burden of the clinical sites to collect the new data
- The adequacy of the funds to be provided to the site for the collection of the additional information

Upon approval by the PLGs, all ancillary study applications must be approved by the PTC Operations Committee. To ensure that timeliness of feedback can be provided, any ancillary study application must be submitted to the PTC Operations Committee one month prior to any submission deadline.

All ancillary studies must acknowledge the PLG and the PTC in any publication or presentation related to the ancillary study.

Any approved ancillary study to a PLG has access to resources available through the NEMO (e.g., biospecimen repository). During the development of the ancillary study application the ancillary study investigators should contact the NEMO to identify needs and associated costs.

Once funding for the ancillary study has been secured and before the ancillary study is to be implemented, the protocol must be review and approved by the PTC Data and Safety Monitoring Board.

19.6 NEMO Site Monitoring

Given the NEMO/Site relationship, monitoring conducted by the NEMO focuses on human subject protection and compliance, and secondarily, on site performance. NEMO monitoring efforts employ a three-tiered approach —remote monitoring, quarterly performance reporting by the PLGs, and on-site monitoring.

Monitoring visits occur on a rolling basis using a risk based monitoring approach.

19.6.1 On-Site Monitoring Visit Procedures

Site Monitoring Visits (SMV) are conducted in accordance with applicable sections of Title 21 of the CFR as outlined below. If future PTC studies are performed under IND/IDE regulation these are expanded to meet those requirements.

The objectives are to:

- Document and report on clinical study progress
- Document that the protocol and associated forms are current
- Update the site team of any changes in study conduct/documentation
- Ensure PTC requirements and investigator obligations are met
- Ensure continued acceptability of the Investigator, his/her team, and facility
- Ensure adequate IP inventory and storage, including ensuring that only trained personnel dispense and administer study drug

Prior to an SMV the Site Monitor:

- Contacts the Site Investigator or Study Coordinator to schedule a date and time for the visit. A proposed schedule is provided including a list of documents to be reviewed, outstanding issues requiring resolution and the study personnel required at the visit
- After scheduling a letter is sent to the Site PI and site personnel confirming date, time, and location of the visit, the purpose of the visit, the site personnel who are required to attend and contact information for the Site Monitor. A copy of this letter is retained in the TMF and should be placed in the site regulatory binder

- Review the regulatory tracking information maintained by the NEMO and listing any outstanding essential documents
- Review previous visit reports, correspondence, serious adverse event forms, and any other relevant material, and prepare a list of outstanding issues that require resolution

The Site Monitor performs the following monitoring activities during the SMV:

- Review the Site Regulatory Binder
 - a. Sign and Date the Monitoring Visit Log each day of the visit
 - b. Verify that all required study documents are present in their current and prior versions
 - c. Retrieve any new or revised essential regulatory documents
 - d. Provide the site with copies of any missing documents
- Safety Reporting
 - a. Confirm that all AE/SAE's have been reported to the IRB and sponsor, as required
 - b. Verify submission of safety reports and DSMB reports to the IRB, as appropriate
- Investigator and Site Personnel Responsibilities
 - a. Review the Staff Signature and Delegation of Responsibilities Log, ensure that it is complete and up-to date. If revisions have been made, obtain a copy
 - b. Review Site PI and site personnel responsibilities with the appropriate site personnel as applicable
 - c. Verify that the Site PI and site personnel are adhering to the protocol and conducting the study according to FDA regulations, ICH GCP and any applicable regulatory requirements
 - d. Provide and document any needed Site PI and site personnel training
- Laboratory and Outcome Measure Supplies
 - a. Verify that laboratory certifications and reference ranges are current and present in the site regulatory binder
- Investigational Product (IP)
 - a. Review IP records
 - b. Verify that IP storage conditions are secure and acceptable
- Facilities Review
 - a. Conduct ongoing review/assessment of the facilities, ensuring that the facility of facilities remain adequate for study participation
 - b. Ensure that the site has adequate clinical trial materials and that storage conditions are secure and adequate
 - c. Review temperature and shipping documentation of biosamples
- Visit Conclusion
 - a. Meet with Site PI and site personnel to ensure they are adequately informed about the trial
 - b. Discuss any site deficiencies or outstanding items

After Each SMV the Site Monitor:

- Places any documents obtained during in the SMV in the TMF and logs them into the NEMO Regulatory Tracking System
- Provides a SMV report to the NEMO PIs, PLG PIs, TMF, Site PI, and site personnel listing any pending actions and any general concerns
- Work with the Site PI and site personnel to resolve any pending actions

Provide guidance to the communication committee regarding frequent issues identified at SMVs. These may be placed in newsletters.

19.7 Study Close-out

19.7.1 Site Responsibilities

The NEMO distributes the study closure checklist and study closure plans to the site as they are developed by the PLGs. Sites work directly with the PLG regarding any data entry, cleaning, or sign-off that is required. Elements of the closure checklist that deal with regulatory matters are communicated to and tracked by the NEMO.

19.7.1.1 Long-Term Storage of Study Records

No study records are permitted to be destroyed without prior written authorization from the PTC Operations Committee. For studies conducted under an Investigational New Drug Application (IND), investigators must retain study records for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and the Food and Drug Administration (FDA) is notified (21 CFR 312.62). For studies not under an IND, investigators must retain study records for a minimum of three years. The three-year time period begins when the primary analysis has been completed.

19.7.1.2 Sample Storage/Destruction

Prior to the destruction of any samples collected within the PTC, the NEMO PI and NIH must be notified of the intention to destroy the samples.

20.0 APPENDICES

Licensed Instruments and Questionnaires

The University of California, San Diego Shortness of Breath Questionnaire (SOBQ): Self-administered rating of dyspnea associated with activities of daily living (ADLs).

12-Item Short Form Health Survey Version 2 (SF-12v2): Subjective measure functional health and well-being.

Fatigue Severity Scale (FSS): Measures fatigue severity in a variety of medical and neurologic disorders.

ICEpop Capability Measure for Older People (ICECAP-O): Measure of capability-wellbeing in older people used in economic evaluation.

EuroQol 5 Dimension Questionnaire (EQ-5D): Visual analog score to assess general health status.

Leicester Cough Questionnaire (LCQ): Self-completed health related quality of life measure of chronic cough.