Study Title:	**Study of Clinical Efficacy of Antimicrobial Therapy Strategy Using Pragmatic Design in Idiopathic Pulmonary Fibrosis (CleanUP-IPF)**
NCT Number:	**NCT02759120**
Document Description:	**Study Protocol**
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Study Protocol

Study of Clinical Efficacy of Antimicrobial Therapy Strategy Using Pragmatic Design in Idiopathic Pulmonary Fibrosis (CleanUP-IPF)

Protocol Amendment 2

Protocol Version Date: March 2, 2018

ClinicalTrials.gov ID: NCT02759120

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1. EXECUTIVE SUMMARY

Title:	***Study of Clinical Efficacy of Antimicrobial Therapy Strategy Using Pragmatic Design in Idiopathic Pulmonary Fibrosis (CleanUP-IPF)***
Location:	Approximately 30-40 clinical sites in the United States
Objectives:	To compare the impact of an antimicrobial therapy strategy on clinical outcomes (hospitalization or death)
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 ≥ 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

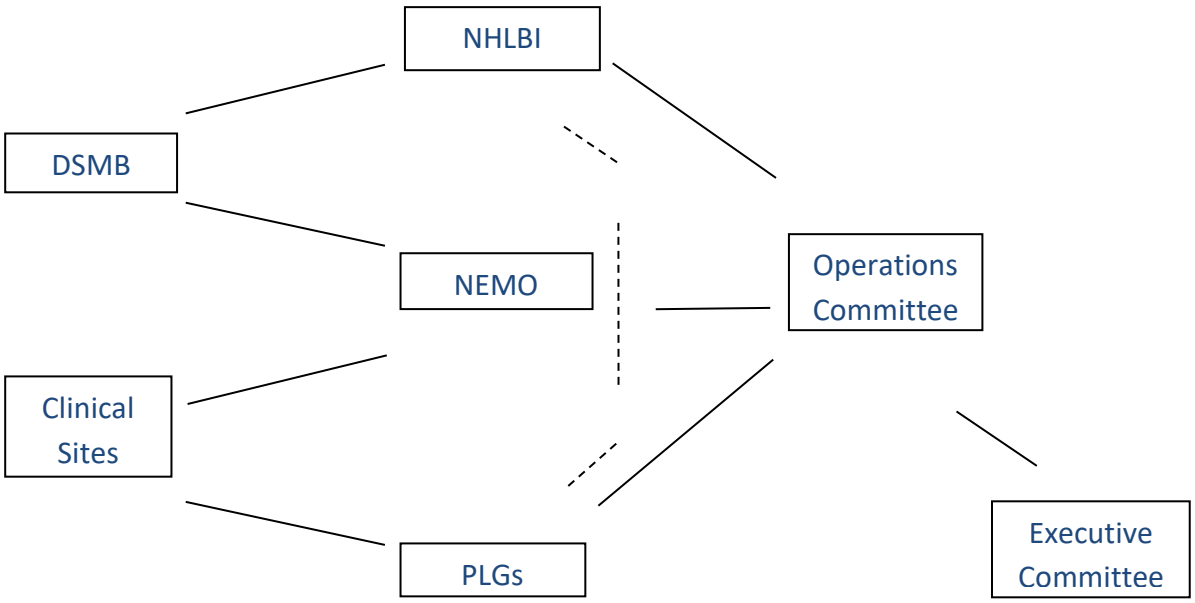
	• Change in DLCO from randomization to 12 months • Total respiratory infections • Change in UCSD-Shortness of Breath Questionnaire and Fatigue Severity Scale score from randomization to 12 months • Change in Leicester Cough Questionnaire score from randomization to 12 months • Change in EQ-5D score and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

Overview of the Pulmonary Trials Cooperative and the CleanUP-IPF study

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

2. HYPOTHESES AND OBJECTIVES

2.1 Primary Objective and Hypothesis

The **primary objective** of the **CleanUP-IPF** study is to compare the effect of standard care vs. standard care plus antimicrobial therapy (co-trimoxazole or doxycycline) on clinical outcomes in patients diagnosed with idiopathic pulmonary fibrosis.

Our **overall hypothesis** is that reducing harmful microbial impact with antimicrobial therapy will reduce the risk of non-elective, respiratory hospitalization or death in patients with IPF.

2.2 Secondary Objectives

Secondary objectives of this protocol will be to examine the effect of this treatment strategy for the following 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 number of respiratory infections
- Change in UCSD-Shortness of Breath Questionnaire from randomization to 12 months
- Change in 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

3. BACKGROUND AND RATIONALE

Idiopathic pulmonary fibrosis (IPF), a fibrotic interstitial lung disease characterized by the histopathologic pattern of usual interstitial pneumonia (UIP), has a median survival of 3-5 years' post-diagnosis but exhibits heterogeneous longitudinal disease progression. Recent studies of pirfenidone and nintedanib confirm beneficial effects on longitudinal change in forced vital capacity but inconsistent benefits on clinical endpoints or health status. Both of these agents can be difficult to tolerate and are expensive.

A recent study showed that an abnormal lung microbial community is independently associated with disease progression in IPF subjects (COMET)[1]; this has been confirmed by a second investigative group[2]. Similarly, it has been demonstrated that polymorphisms in the TOLLIP gene are associated with impaired outcome in IPF patients[3]. Additional preliminary data suggest that a systemic marker of inflammatory cell activation is associated with IPF disease progression[4]. Lastly, preliminary data from COMET suggest that a circulating gene expression signature of altered host response is associated with the aberrant lung microbial community. Intriguingly, other investigative groups have suggested improved clinical outcomes in IPF patients treated with co-trimoxazole or doxycycline compared to matched placebo[5-7]. The totality of these data suggests that an abnormal lung microbiome interacting with genetic susceptibility in host response may be associated with impaired clinical outcomes in IPF.

Our principal hypothesis is that antimicrobial therapy in IPF patients will improve clinical outcomes in a pragmatic therapeutic trial. The study aims are:

Aim 1. To determine if antimicrobial therapy (co-trimoxazole or doxycycline) in addition to standard care compared to standard care alone improves the time to non-elective respiratory hospitalization or death.

Aim 2. To determine if response to antimicrobial therapy is a function of genetic susceptibility to impaired host response in IPF patients.

We propose to examine the potential of precision medicine by examining the interaction of antimicrobial therapy with baseline genotype. Our long-term goal is to define patient-specific therapy in IPF.

4. STUDY POPULATION AND ELIGIBILITY CRITERIA

4.1 Inclusion Criteria

1. ≥ 40 years of age
2. Diagnosed with IPF by enrolling investigator
3. Signed informed consent

4.2 Exclusion Criteria

1. Received antimicrobial therapy in the past 30 days for treatment purposes (antibiotic prophylaxis for procedures do not meet criteria, nor do antivirals)
2. Contraindicated for antibiotic therapy, including but not exclusive to:
    a. Allergy or intolerance to BOTH tetracyclines AND trimethoprim, sulfonamides or their combination
    b. Allergy or intolerance to tetracyclines AND known potassium level > 5 mEq/L in the past 90 days.
        i. If the enrolling physician feels the potassium level has normalized, documentation to that effect must be provided.
    c. Allergy or intolerance to tetracyclines AND concomitant use of angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), potassium sparing diuretic, dofetilide, methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide
    d. Allergy or intolerance to tetracyclines AND known glucose-6-phosphate dehydrogenase deficiency
    e. Allergy or intolerance to tetracyclines AND untreated folate or B12 deficiency
    f. Allergy or intolerance to tetracyclines AND known renal insufficiency (defined as a GFR < 30 ml/min within the previous 90 days)
        i. If the enrolling physician feels the renal dysfunction has resolved, documentation to that effect must be provided.
    g. Seizure disorder on antiepileptic therapy.
3. Pregnant (as determined by urine dipstick pregnancy test at randomization), or anticipate becoming pregnant
4. Use of an investigational study agent for IPF therapy within the past 30 days, or an IV infusion with a half-life of four (4) weeks
5. Concomitant immunosuppression with azathioprine, mycophenolate, cyclophosphamide, or cyclosporine.

Participation in other IPF clinical trials or registries, while participating in the CleanUP-IPF trial, is not exclusionary assuming the participant meets all other eligibility criteria.

5. 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.

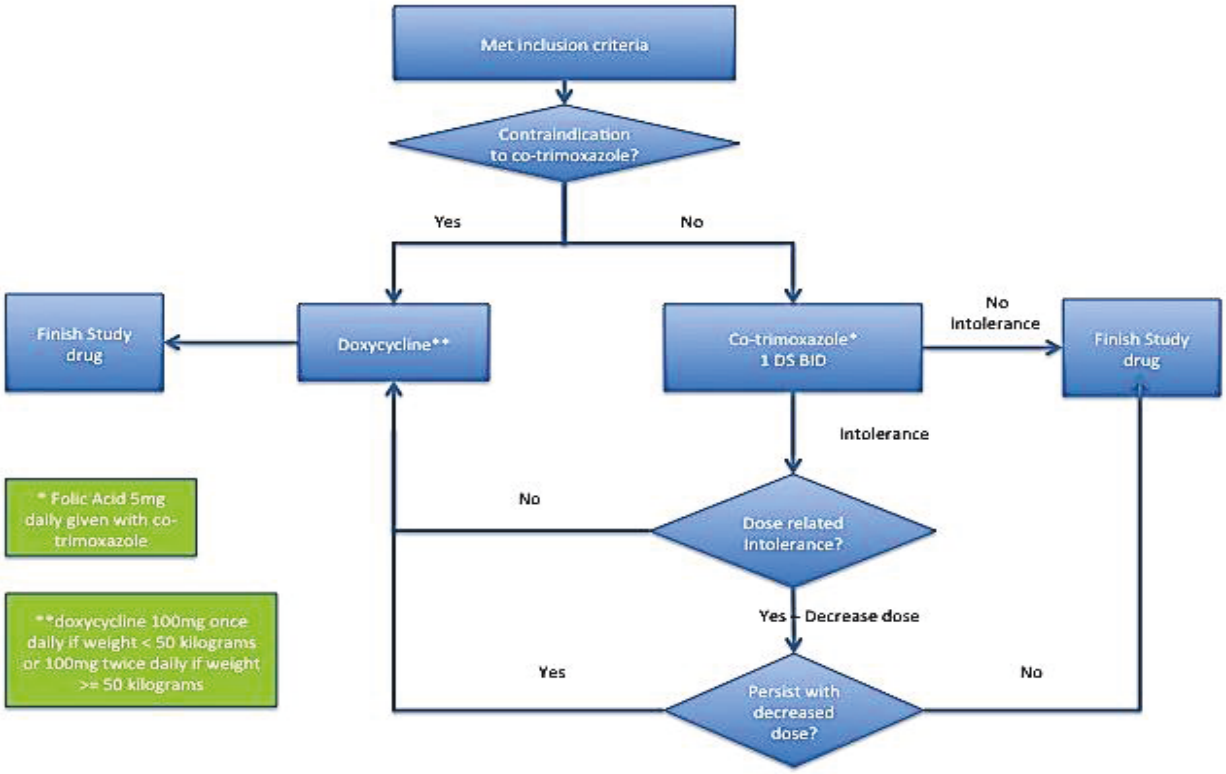
Figure 1 illustrates the proposed antimicrobial therapy algorithm. Contraindications to co-trimoxazole at enrollment include:

- 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, 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



5.1 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.

5.2 Blinding

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.

5.3 Patient Safety and Concomitant Therapies

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 factors[10]. Our inclusion/exclusion criteria should mitigate this risk as will monitoring for hyperkalemia early after the introduction of co-trimoxazole therapy[10].

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 ≥ 50 kg, and no 5mg folic acid will be prescribed.

6. RECRUITMENT AND SCREENING PROCEDURES

6.1 Common Recruitment/Screening Procedures

All patients diagnosed at the participating centers with IPF will be screened by a study coordinator. Patients meeting eligibility criteria will be approached regarding participation in this study.

6.2 Estimated Enrollment Period

This study will enroll approximately 500 patients at 20-40 study sites. The projected enrollment timeline for enrollment is approximately 30 months.

7. SCREENING EVALUATIONS AND RANDOMIZATION

A complete schedule of assessments throughout the study is given in Appendix A.

7.1 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.

7.2 Screening Assessments

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.

7.3 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.

8. 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.

8.1 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**)

8.2 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

8.3 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)

8.4 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

8.5 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

8.6 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 (<u>for antimicrobial arm only</u>):

- 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

8.7 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

8.8 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

8.9 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

8.10 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.

9. OUTCOME DETERMINATIONS

9.1 Primary Endpoint

The primary endpoint of this study will be the time to first non-elective, respiratory hospitalization or all-cause mortality.

9.2 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 number of respiratory infections
- Change in UCSD-Shortness of Breath Questionnaire from randomization to 12 months
- Change in 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

9.3 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. PARTICIPANT SAFETY AND ADVERSE EVENTS

10.1 Institutional Review Boards

All CleanUP-IPF sites will submit the study protocol, informed consent form, and other study documents to their IRB for approval—the approval letter for each clinical center will be stored at the CC. Any amendments to the protocol, other than minor administrative changes, must be approved by each IRB before they are implemented.

10.2 Informed Consent

All patients will have the purpose of the study, the study interventions and evaluations, and the potential risks and benefits of participation explained to them and their questions answered. If they consent to participation in this study, they will review and sign the informed consent form.

10.3 Summary of the Risks and Benefits

This study will evaluate an antimicrobial therapy strategy in patients with IPF. These agents are currently used in clinical practice. We therefore do not anticipate that participation in this study will be associated with increased risks beyond that of standard IPF therapy. We have added limited exclusionary criteria to minimize risk of antimicrobial therapy.

Potential benefits to study participants include the possibility of improvements in clinical outcomes.

10.4 Adverse Events

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.

10.5 Serious Adverse Events

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

10.6 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 pregnancy test will be completed.

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 (™), sold for emergency use after unprotected sex, are not acceptable methods for routine use.

11. STATISTICAL CONSIDERATIONS

11.1 Overview

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).

11.2 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 (pp), baseline FVC (pp), 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.

11.3 Sample Size Justification

Based on prior work from the study team using IPFnet data, it is anticipated that the event rate in the placebo arm will be highly dependent on the proportion of patients enrolled at the different GAP scores. Given the availability of two FDA-approved drugs for IPF, it is our belief that the study population will be heavily weighted toward GAP scores of 3. In **Table 1**, the statistical power is determined for designs enrolling 500 patients with placebo group events rates varying from 24% to 36% and (12-month) treatment effects varying from 30% to 35%. In

general, the proposed design provides adequate power expect when the 12-month standard-of-care group event rate is 24% and the reduction in events is less than 30%.

Table 1. Statistical Power Assuming a Sample Size of 500 Randomized Patients

Standard-of-care event rate*	Antimicrobial therapy strategy event rate*	One-year Event Rate Reduction	Power
24%	16.8%	30%	78%
30%	21.0%	30%	87%
36%	25.2%	30%	93%
24%	16.0%	33.3%	86%
30%	20.0%	33.3%	93%
36%	24.0%	33.3%	97%
24%	15.6%	35%	89%
30%	19.5%	35%	95%
36%	23.4%	35%	98%

*12-month event rates. Calculations assume a 2-sided Type-I error rate of 0.05. The minimum follow-up is planned to be 12 months and the maximum follow-up is 42 months. Drop-out rates are assumed to be approximately 2% per year. Power calculations were based on a log-rank test with assumed event rates were exponentially distributed. Calculations were computing using nQuery 7.0 software.

We plan to enroll 500 patients over a 30 month window with a minimum of 12 months of follow-up on all patients. **Table 2** shows the required number of endpoint events to have 80% to 90% power with hazard ratios varying from 0.50 to 0.75.

Table 2. Required number of events

	HR=0.50	HR=0.55	HR=0.60	HR=0.65	HR=0.70	HR=0.75
80% power	65	88	120	169	247	379
85% power	75	100	138	194	282	434
90% power	87	118	161	226	330	508

Calculations performed using nQuery 7.0 and assume a 0.05 type I error rate (two-sided) with 1:1 randomization.

11.4 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.

12. DATA MANAGEMENT PROCEDURES

12.1 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.

12.2 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.

12.3 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.

12.4 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.

12.5 Data Editing

Completed data will be entered into the IBM Clinical Development system. If incomplete or inaccurate data are found, a data clarification request 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 data management system and will adhere to the data entry and query response timelines specified by the CleanUP-IPF PLG.

12.6 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.

13. STUDY ADMINISTRATION

13.1 Data and Safety Monitoring Board

A DSMB will be appointed by the NHLBI for this trial. It will include individuals with pertinent expertise in IPF and clinical trials. The DSMB will advise the Steering Committee regarding the continuing safety of current participants and those yet to be recruited. It is anticipated that the DSMB will meet approximately 2 times per year to review safety and overall study progress.

13.2 Statistical Monitoring Plan

Safety and efficacy data will be periodically assessed by the DSMB. Safety and efficacy data will be periodically assessed by the DSMB. For ethical reasons, an interim examination of key safety and endpoint data will be performed at regular intervals during the course of the trial. The interim monitoring will also involve a review of the control arm event rates, patient recruitment, compliance with the study protocol, status of data collection, and other factors that reflect the overall progress and integrity of the study. An NHLBI-appointed DSMB will carefully and confidentially review the results of the interim analyses and status reports. If protocol modifications are warranted, close consultation among the DSMB, the NHLBI staff, and the study leadership will be required. A separate DSMB charter outlining the operating guidelines for the committee and the protocol for evaluation of data will be created prior to study enrollment and agreed upon during the initial meeting of the DSMB.

It is anticipated that the DSMB will meet at 6-month intervals to review the accumulating data. The DCRI will create regular reports to track patient enrollment reports, rates of compliance with the assigned testing strategy, and frequency of protocol violations. Prior to each meeting, the data coordinating center will conduct any requested statistical analyses and prepare a summary report along with the following information: patient enrollment reports, rates of compliance with the assigned testing strategy, frequency of protocol violations, and description of SAEs (statistical comparisons of the randomized arms with respect to these SAEs will use chi-square or other appropriate 2-sample methods).

There will be one planned interim review for efficacy. The efficacy review will focus on the composite endpoint of respiratory hospitalization or all-cause death and should occur once 300 enrolled subjects have been followed for 12 months. The Lan-DeMets alpha spending function with O'Brien-Fleming type boundaries will be used for the interim analysis.

13.3 Site Training Requirements

Clinical sites participating in this study will be trained in the following aspects of the study including a protocol overview covering:

- 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

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15. APPENDIX A – Schedule of Assessments

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]		X[3]		X[3]		
Chemistry panel w/liver function tests	X (if not available in last 90 days)			X[3]	X[3]		X[3]		X[3]		
Electrolytes only		X[2]									
Genotype	X										
Gene expression	X						X		X		
Buccal Swab, Fecal samples	X						X		X		
Patient Reported Outcomes Questionnaires[1]	X						X		X		
Clinical Events Mortality Hospitalization Resp. infection			X X X			X X X	X X X	X X X	X X X	X X X	X X X

1. Patient reported questionnaires include: UCSD-SoBQ, Fatigue Severity Scale, Leicester Cough, EQ-5D, SF-12, ICECAP-O
2. For subjects receiving co-trimoxazole, a blood sample to document electrolytes will be drawn at week 1, Visit 1A.
3. For subjects assigned to the antimicrobial therapy arm, a blood sample to document complete blood count, liver function tests, and chemistry panel, will be drawn at 3 months, 6 months, 12 months, and 24 months to be obtained at Visit 2A, Visit 2B, Visit 4, and Visit 6, respectively.

16. APPENDIX B – CleanUP-IPF Laboratory Schedule

Antimicrobial Arm (Co-trimoxazole and Doxycycline Arms)

	CBC	Electrolytes	Chemistry plus liver function tests	Gene expression	Genotype	Buccal sample	Fecal sample	Approx. total Blood Amount
Baseline	x		x	x	x	x	x	28.5 ml
Week 1		x*						6 ml
3 month	x		x					8.5 ml
6 month	x		x					8.5 ml
12 month	x		x	x		x	x	18.5 ml
24 month	x		x	x		x	x	18.5 ml
								88.5 ml

***only in co-trimoxazole treated patients**

Standard of Care Arm

	CBC	Chemistry plus liver function tests	Gene expression	Genotype	Buccal sample	Fecal sample	Approx. total Blood Amount
Baseline	x	x	x	x	x	x	28.5 ml
12 month			x		x	x	10 ml
24 month			x		x	x	10 ml
							48.5 ml

Safety Labs

Complete Blood Count (CBC): WBC, RBC, hemoglobin, hematocrit, mean corpuscular volume (MCV), Platelets, mean platelet volume (MPV)

Electrolytes: Sodium, Potassium, Chloride, Carbon Dioxide (CO_2)

Chemistry: Sodium, Potassium, Chloride, Carbon Dioxide (CO_2), Urea Nitrogen (BUN) and Creatinine

Liver Function Studies: Alkaline Phosphatase, Total Bilirubin, Direct bilirubin, Aspartate Aminotransferase (AST), and Alanine Aminotransferase (ALT)