



**ACE-IPF**  
**ANTICOAGULANTEFFECTIVENESSINIDIOPATHICPULMONARYFIBROSIS**  
*A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL*

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**Protocol Summary**

PRODUCT	Warfarin
CLINICALTRIALS.GOV IDENTIFIER	NCT00957242
PROTOCOL TITLE	Anticoagulant Effectiveness in IPF (ACE-IPF)
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Confirmed idiopathic pulmonary fibrosis
STUDY OBJECTIVES	To demonstrate reduced time to composite endpoint (all-cause mortality, or non-elective, non-bleeding hospitalization or a decrease in absolute forced vital capacity (FVC) of 10% or greater from baseline) in subjects with idiopathic pulmonary fibrosis treated for 48 weeks with warfarin compared with placebo.
STUDY DESIGN	Multi-center, randomized, double-blind, placebo-controlled
TREATMENT REGIMEN	Warfarin daily titrated to an international normalized ratio (INR) of 2.0-3.0 or matched placebo daily for 48 weeks
ROUTE OF ADMINISTRATION	Oral
INTERVAL BETWEEN FIRST AND LAST DOSES OF ACTIVE STUDY AGENT	48 weeks
DURATION OF STUDY PARTICIPATION	54 weeks
END OF STUDY DEFINITION	54 weeks
NUMBER OF SUBJECTS	256 (1:1 randomization)
NUMBER OF SITES	Approximately 22 U.S. sites
PRIMARY ENDPOINTS	Time to composite endpoint (time to death or non-elective, non-bleeding hospitalization, drop in FVC $\geq$ 10% absolute)
SECONDARY ENDPOINTS	Difference in mortality between treatment and control groups  Difference in mortality + hospitalizations between treatment and control groups.  Difference in all-cause hospitalizations between treatment and control groups

	<p>Change in FVC between treatment and control groups</p> <p>Global ranking difference between treatment and control groups</p> <p>Difference in minor and major bleeding events between treatment and control groups</p> <p>Difference in acute exacerbations between treatment and control groups</p> <p>Difference in respiratory-related hospitalizations between treatment and control groups</p> <p>Difference in cardiovascular mortality or morbidity (acute myocardial infarction (AMI), cerebral vascular accident (CVA), venous thromboembolism (VTE)) between treatment and control groups</p> <p>Difference in 6-minute walk distance (6MWT) between treatment and control groups</p> <p>Difference in quality of life (QOL) assessments between treatment and control groups</p> <p>Difference in diffusing capacity of the lung for carbon monoxide (DLCO) and lung volumes between treatment and control groups</p> <p>Biological Response Monitoring (Fibrin D dimer)</p>
<p>INTERIM ANALYSIS</p>	<p>Summaries of the serious adverse events will be reviewed each month. More detailed safety data will be reviewed every 6 months.</p>

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*List of Abbreviations*

6MWD	6-minute walk distance
6MWT	6-minute walk test
ABG	arterial blood gas
ACE-IPF	Anti-Coagulant Effectiveness in Idiopathic Pulmonary Fibrosis
AE	adverse event
ALI	acute lung injury
AMI	acute myocardial infarction
ASA	acetylsalicylic acid / aspirin
AV	atrioventricular
BDS	Borg dyspnea scale
CRF	case report form
CT	computed tomography
CVA	cerebral vascular accident
CXR	chest x-ray
DCC	Data Coordinating Center
DCF	data clarification form
DLco	diffusing capacity of the lung for carbon monoxide
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
FDA	Food and Drug Administration
FDP	fibrin-degradation product
FVC	forced vital capacity
GCP	Good Clinical Practice
GI	gastrointestinal
HHS	Health & Human Services (U.S. Dept . of)
HIPAA	Health Insurance Portability and Accountability Act
HRCT	high-resolution computed tomography
IFN $\gamma$ -1b	interferon gamma-1b
ILD	interstitial lung disease
INR	international normalized ratio
IPF	idiopathic pulmonary fibrosis
IPFnet	Idiopathic Pulmonary Fibrosis Clinical Research Network

IRB	institutional review board
IVRS	interactive voice response system
MCP	monocyte chemotactic protein
MI	myocardial infarction
MMP	matrix metalloproteinase
MMRM	mixed model repeated measure
MOOP	Manual of Operating Procedures
NHLBI	National Heart Lung and Blood Institute
NIH	National Institutes of Health (U.S.)
NSAID	non-steroidal anti-inflammatory drug
NSIP	nonspecific interstitial pneumonia
NYHA	New York Heart Association
PA	arterial pressure
PAI	plasminogen activator inhibitor
PaO <sub>2</sub>	partial pressure of arterial oxygen
PAP	pulmonary artery pressure
PBMC	peripheral blood mononuclear cell
PFT	pulmonary function test
PHS	Public Health Service (U.S.)
PI	principal investigator
QOL	quality of life
SAE	serious adverse event
SAP	statistical analysis plan
SpO <sub>2</sub>	oxygen saturation measured using pulse oximetry
TAT	thrombin-antithrombin III complex
TIA	transient ischemic attack
<i>t.i.d.</i>	three times a day
UCSD SOBQ	University of California at San Diego Shortness of Breath Questionnaire
UIP	usual interstitial pneumonia
VTE	venous thromboembolism
WHO	World Health Organization



## **A Introduction**

### **A1 Study Abstract**

This is a randomized, double-blind, placebo-controlled trial designed to assess the safety and efficacy of warfarin in patients with idiopathic pulmonary fibrosis (IPF).

Approximately 256 patients who have been diagnosed with IPF and have failed standard-of-care treatments will be enrolled. The study will employ a 2-arm design with 1:1 randomization to warfarin or placebo. Each subject will be treated and followed for 48 weeks. The primary endpoint is time to achievement of a composite endpoint of 1) all-cause mortality or 2) decrease in the absolute FVC > 10 % from baseline or 3) non-elective hospitalization (exclusive of hospitalizations for bleeding). A separate safety assessment of major and minor bleeding events will also be evaluated.

This clinical trial will be performed as part of the National Institutes of Health (NIH)/National Heart Lung and Blood Institute (NHLBI)-sponsored Idiopathic Pulmonary Fibrosis Clinical Research Network (IPFnet).

### **A2 Primary Hypothesis**

Treatment with warfarin will improve clinical outcomes in patients with IPF.

### **A3 Purpose of the Study Protocol**

To demonstrate improved clinical outcomes in subjects with IPF treated for 48 weeks with warfarin compared with placebo.

## **B Background**

### ***B1 Prior Literature and Studies***

Animal models of lung injury and fibrosis amply demonstrate a pathogenic role for the coagulation/fibrinolytic cascades. Both human studies and experimental animal models of lung injury and fibrosis overwhelmingly demonstrate an increase in pro-coagulant activity (tissue factor/VIIa), and a suppression of the normal fibrinolytic activity through up-regulation of protease inhibitors (plasminogen activator inhibitor, PAI-1;  $\alpha$ -2-antiplasmin) in the alveolar compartment.(1-5) Similar findings have been observed in the alveolar compartment of patients with sarcoidosis, IPF, and acute lung injury (ALI).(6-10) These coagulation/fibrinolytic cascade derangements explain the accumulation of fibrin noted in alveolar space in association with areas of active fibrosis in IPF (fibroblastic foci).(11) In vitro and in vivo evidence is emerging that indicates that these same coagulation factors may have effects on inflammation and matrix remodeling that extend beyond the formation and dissolution of fibrin.(12-15) These inflammatory and matrix remodeling effects are largely mediated by intracellular signaling pathways that are initiated through activation of protease activated receptors.(12, 14, 16) The pleiotropic effects of coagulation factors would argue strongly in favor of pursuing anticoagulation treatment as a therapeutic target for IPF.

A prospective study comparing anticoagulation/prednisolone (warfarin to INR of 2-3 and Dalteparin during “exacerbations”) to prednisolone alone in 56 patients with IPF shows promising results.(17) The mean FVC of the cohort was approximately 70% of predicted, and the mean DLCO was 60–65% of predicted, indicating “early disease”. This study demonstrated a significant survival benefit of anticoagulation/prednisolone (Hazard Ratio = 2.9; 95% CI 1.0 – 8.0) with a 1-year survival of 58% in the control group vs. 87% in the anticoagulation group. Although this study was small and un-blinded, it provides published evidence of a robust survival benefit for anticoagulation therapy in human IPF. We propose to extend these findings in a rigorously-designed, double-blinded, multi-center trial in the US.

## ***B2 Rationale for this Study***

The rationale for selecting warfarin as the study agent can be expressed in two parts, scientific plausibility and practical consideration of the agent. In the spirit of the original Request for Application, the IPFnet Steering Committee aims to study an agent that might prove efficacious, while selecting an agent that is also not likely to be a candidate for extramural support. The IPFnet Steering Committee generated the additional agent selection criteria of proven safety in long term administration in humans, with a preference for agents used in patients with IPF. Numerous specific anticoagulant agents were considered; however, warfarin best fit the stated criteria.

As an FDA-approved agent, there is a thorough experience with its side effect profile over decades of use. Warfarin has been successfully used in numerous long term trials, and it is readily available at minimal cost. The potential beneficial effects of warfarin in an IPF population make warfarin the clear agent of choice.(17)

## **C Study Objectives**

### ***C1 Primary Aim***

To demonstrate improved outcomes in subjects with IPF treated for 48 weeks of warfarin compared with placebo. The primary endpoint associated with this primary aim is the time to attainment of the composite endpoint of:

1. All cause mortality  
OR
2. Non-elective hospitalization (exclusive of hospitalizations for bleeding)  
OR
3. Decrease in the absolute FVC  $\geq 10\%$  from baseline

### ***C2 Secondary Aims***

The secondary endpoints for this study are as follows:

1. Difference in mortality between treatment and control groups

2. Difference in mortality plus all-cause hospitalizations between treatment and control groups
3. Difference in all-cause hospitalizations and resource use between treatment and control groups
4. Change in FVC between treatment and control groups
5. Global ranking difference\* between treatment and control groups
6. Difference in bleeding events between treatment and control groups
7. Difference in acute exacerbations (as defined in the ACE-IPF Manual of Operating Procedures) between treatment and control groups
8. Difference in respiratory-related hospitalizations between treatment and control groups
9. Difference in cardiovascular mortality or morbidity (AMI, CVA, VTE) between treatment and control groups
10. Difference in 6MWT between treatment and control groups
11. Difference in QOL assessments between treatment and control groups
12. Difference in dyspnea test between treatment and control groups
13. Difference in DLCO and lung volumes between treatment and control groups
14. Difference in biological response (Fibrin D-dimer)

\*The global ranking system is a clinical composite end-point sequentially ranking subjects based on 3 outcome tiers of decreasing clinical importance: **Tier 1**: time to death within 48 weeks; **Tier 2**: among those alive at 48 weeks, time to acute exacerbation or non-elective/non-bleeding hospitalization within 48 weeks; **Tier 3**: among those without events in Tiers 1 and 2, the change in FVC from enrollment to 48 weeks.(18)

### ***C3 Prespecified Subgroups of Interest***

Treatment effects will be estimated and compared within key subgroups:

- Patients with a history of coronary artery disease, pulmonary embolism, deep vein thrombosis, or cerebral vascular accident
- Patients taking prednisone at enrollment
- Patients on concomitant FDA-approved treatment for IPF at enrollment
- Patients with a DLCO < 35% (adjusted for hemoglobin) at enrollment

### ***C4 Rationale for the Selection of Outcome Measures***

The optimal study design of a therapeutic trial in IPF would have survival as the stand alone primary endpoint. Given the relatively low mortality expected in an IPF population including patients with similar inclusion and exclusion criteria, the required sample size and duration of follow-up are beyond the resources of the IPFnet. For example, the recently completed Phase 3 IFN- $\gamma$  1b (GIPF-007; INSPIRE) study was a survival-based

study and anticipated recruitment of more than 800 subjects at 75 centers worldwide with more than two years of follow up for each subject (FDA Public Health Advisory 2007). As such, within the context of the current IPFnet trial, survival alone is an impractical primary endpoint variable.

The Japanese study which showed a mortality benefit in IPF patients included both time to death as well as time to re-hospitalization (Kubo et al., 2005). It showed 1-year hospitalization-free rates of 74% in the anticoagulant group and only 39% in the control group (p=0.3). Although this result was not statistically significant given the small sample size, it suggests that anticoagulation therapy may increase time to hospitalization.

Several groups have published data defining an appropriate surrogate outcome variable based on changes in longitudinal measures of FVC. In particular, a 10% decrement in FVC during 6 to 12 months is a powerful predictor of survival in IPF.(18-22)

With strong evidence of FVC progression being related to mortality on a per-subject basis, the IPFnet felt that it was important to include a disease progression component in the overall endpoint, as both a surrogate for mortality but also as a clinical indicator that a different treatment regimen may be appropriate for subjects achieving that endpoint.

We acknowledge that some of the patients recruited into this study will have significant co-morbidities, including pulmonary hypertension, pulmonary embolism, and cardiac disease; however, randomization should balance these factors across the treatment groups.

## **D Investigational Agent**

### ***D1 Clinical Data to Date***

Warfarin has been in wide use as a therapeutic anticoagulant for over 50 years. The safety profile of this agent is well known, and standard processes for monitoring the therapeutic range using the international normalized ratio (INR) have been in place for decades.

## ***D2 Dose Rationale and Risk/Benefits***

The key to the safe therapeutic use of warfarin is the knowledge of subject characteristics (e.g. age, co-morbid diseases, and genetic factors), drug interactions, and changes in diet that affect the metabolism and/or efficacy of warfarin. As not all clinically significant drug/diet interactions have been validated in randomized controlled clinical trials, we will take the expert-suggested approach of increasing the frequency of INR checks to twice weekly in the event of any change in medication and/or diet.(23) Further, we will suggest the avoidance of drugs with known level-one evidence for drug-drug interactions or drug-diet interactions and where possible, replace those with suitable alternatives.(23) Due to increased risk of bleeding, patients on long-term (> 30 day) therapy of clopidogrel plus aspirin, as well as patients on prasugrel, are excluded. Patients taking clopidogrel alone or taking between 81 and 325 mg aspirin without clopidogrel are acceptable, although the expected bleeding risk will increase from approximately 1% to 2% per 100 patient years compared to those not on aspirin.(24, 25) **However, as noted, any change in diet or medication will be followed by twice per week INR monitoring.**

The choice of the INR target for any study/treatment is always based on a compromise between utilizing an adequate INR to reduce thrombosis and minimizing bleeding risk. Most reports in literature have demonstrated that moderate-intensity anticoagulation with a target INR of 2.0-3.0 is associated with a lower bleeding risk than targeted INR>3.0 without a significant decrease in efficacy.(26, 27) Target INR's of <2.0 show reduced efficacy in preventing recurrent venous thromboembolism with no reduction in bleeding risk, as compared with an INR of 2.0-3.0.(28) Lastly, the clinical trial demonstrating efficacy for improved mortality in IPF utilized a target INR of 2.0-3.0.(17)

Home monitoring INR/self-management has been shown to be superior to physician office monitoring in both randomized and non-randomized studies.(29-31) Home monitoring results in an increased frequency of time in target range, as well as reduced bleeding complications and, in some cases, increased long-term survival.(29-31) Most studies conclude that the advantage of home monitoring is the increased frequency at which the INR is checked in both stable subjects and in those with adjustments in other medications and in diet. In addition, an obvious advantage compared with INR monitoring in an anticoagulation clinic is the ability of subjects to monitor their own INR

with the same reagents/equipment during times of travel. Subjects in the ACE-IPF trial will use an online warfarin management system. This system will utilize encrypted home monitors with internet-based recording, computerized dosing adjustments and phone-in back up.(32-34) This home monitoring system will accomplish the dual purpose of maintaining subject safety as well as adequate blinding. Previous studies of this home monitoring system suggest that a small percentage (< 5%) of subjects is unwilling to perform the finger stick.(33)

The major anticipated complication of warfarin therapy is bleeding. Bleeding risk is a function of several factors including the intensity of anticoagulation effort.

Characteristics of the patients, including age greater than 75, and the presence of malignancy are significant predictors of major bleeding.(35-41) Concomitant medications including aspirin have been shown to increase the bleeding rates from approximately one to two events per 100 person years.(24, 25) Non-steroidal anti-inflammatory drugs (NSAIDs) appear to increase the risk of upper GI bleeding with warfarin.(26) While there are no good randomized, prospective, controlled trials on the effect of NSAID's on anticoagulant related bleeding, we will discourage the use of NSAIDs and replace them with acetaminophen when possible, as has been done in other trials.(42) We will monitor the INR more frequently in the first month and increase subject contact to mitigate the potential effects of beginning therapy and/or unexpected responses to warfarin.

## **E Study Design**

### ***E1 Overview or Design Summary***

This is a randomized, double-blind, placebo controlled, multi-center study that will compare warfarin and placebo in subjects with idiopathic pulmonary fibrosis. Enrolled subjects will undergo a baseline evaluation along with the collection of clinical data and blood samples. Subjects will then be given 5mg of warfarin or matched placebo daily for the first 3 days. The investigator may choose a starting dose < 5mg in cases where concomitant disease state(s) or medications known to increase the sensitivity to warfarin exist.(43) Subsequent dosing will be determined by INR response, or, in the case of placebo patients, an algorithm calculated to mirror a typical warfarin user's INR response. Warfarin or matched placebo treatment will continue for 48 weeks.

## ***E2 Subject Selection and Withdrawal***

### **2.a Inclusion Criteria**

1. Subjects must have a diagnosis of IPF (Section F.1.a). There is no limit from the time of diagnosis to the time of enrollment.
2. Subjects must be between 35 and 80 years of age, inclusive.
3. Subjects must be capable of understanding and signing consent.
4. Subjects must have progressed despite conventional therapy (standard of care).

Progression is defined as follows:

- a. Worsened dyspnea, OR
- b. Physiological deterioration as defined by any of the following:
  - Relative decline in FVC (liters) by  $\geq 10\%$  [(pre-value (-) screen-value) / pre-value] OR
  - Relative decline in DLCO (liters) by  $\geq 15\%$  [(pre-value (-) screen-value) / pre-value] OR
  - Reduction of oxygenation saturation by  $\geq 5\%$  with or without exertion on a constant oxygen administration (room air or with supplemental oxygen), OR
  - Worsened radiographic findings [chest x-ray (CXR) or high-resolution computed tomography (HRCT)]

Verification of physiologic criteria are not required if criteria for worsened dyspnea is met.

Change in physiologic value is over any time period.

The standard of care regimen must be stable for 28 days before enrollment. While participating, subjects will be encouraged to maintain a stable IPF treatment regimen.

### **2.b Exclusion Criteria**

1. Current enrollment in another investigational protocol



2. Current treatment with an investigational drug (i.e., participating in an active investigational drug protocol) within the previous 4 weeks or 5 times the half-life of the investigational agent, whichever is longer, prior to screening
3. Subject is actively listed for lung transplantation at the time of enrollment
4. Subjects who will not be able to perform/complete the study, in the judgment of the physician investigator or coordinator, for at least 3 months. For example:
  - a. Subject has current signs or symptoms of severe, progressive or uncontrolled comorbid illnesses such as: renal, hepatic, hematologic, gastrointestinal, endocrine, cardiac, neurologic, or cerebral disease, or any laboratory abnormality which would pose/suggest a risk to the subject during participation in the study.
  - b. Subject has a transplanted organ requiring immunosuppression
  - c. History of substance abuse (drugs or alcohol) within the 2 years prior to screening, history of noncompliance to medical regimens, inability or unwillingness to perform INR monitoring, or other condition/circumstance that could interfere with the subject's adherence to protocol requirements (e.g. psychiatric disease, lack of motivation, travel, etc).
  - d. Have any known active malignancy or have a history of malignancy within the previous 2 years (an example of an exception is a non-melanoma skin cancer that has been treated with no evidence of recurrence for at least 3 months) that might increase the risk of bleeding.
5. Estimated life expectancy < 12 months due to a non-pulmonary cause.
6. Subject has another respiratory disease that is predominant (as judged by the PI) in addition to IPF.
7. Anticoagulation-related exclusions include:
  - a. Current anticoagulation therapy with warfarin
  - b. Increased risk of bleeding (e.g. uncorrectable inherited or acquired bleeding disorder)
  - c. Platelet count < 100,000 or hematocrit < 30% or > 55%
  - d. History of severe gastrointestinal bleeding within 6 months of screening
  - e. History of CVA within 6 months of screening
  - f. High risks of falls as judged by the PI
  - g. Surgery or major trauma within the past 30 days

- h. Pregnancy, or lack of use of birth control method in women of childbearing age
- i. Any condition that, in the determination of the PI, is likely to require anticoagulation therapy during the study.
- j. Clopidogrel and aspirin combination therapy for > 30 days duration is exclusionary.  
(Aspirin monotherapy [81-325 mg daily] or clopidogrel monotherapy are acceptable. Combination clopidogrel and aspirin  $\leq$ 81mg/day for  $\leq$ 30 days is also acceptable. NSAIDs are discouraged; acetaminophen may be substituted.)
- k. Patients on prasugrel are excluded. Prasugrel must be stopped for one week prior to starting study drug.

Waivers can be applied for on a case-by-case basis if the principal investigator (PI) feels the safety of the subject will not be compromised. The waiver request process is detailed in the ACE-IPF Manual of Operating Procedures (MOOP).

### **2.c Ethical Considerations**

This study has been designed in order to maximize accessibility for patients with IPF. The resources necessary for home monitoring of the INR will be provided to subjects to ensure that no one is barred from participation due to lack of infrastructure or financial constraints.

### **2.d Subject Recruitment Plans and Consent Process**

Subjects for this study will be recruited from those physician-referred or self-referred at participating centers in the IPFnet. Special recruitment strategies will be employed to target ethnic minorities. We will attempt to recruit male and female subjects into the study.

All IPFnet subjects will provide written informed consent using procedures reviewed and approved by each clinical center's IRB. Informed consent will be administered in person by study personnel. No study procedures will be conducted until the signed documents have been provided to the IPFnet clinical center.

Sample informed consent documents are provided to the clinical centers but will be modified according to the specific needs of the IRB at each participating clinical center.

## **2.e Randomization Method and Blinding**

A permuted-block randomization scheme will be created with varying block sizes stratified by clinical center and screening DLCO (adjusted for hemoglobin). Stratification on DLCO will be between patients < 35% of predicted and those  $\geq$  35% of predicted. Once a subject has completed the screening and baseline period and evaluation for inclusion/exclusion criteria, the randomization process will begin. Subjects will be randomized to receive one of the two treatment regimes with equal probability (1:1), via telephone contact with a central interactive voice response system (IVRS), using a toll-free randomization number. On the day of randomization, after the subject has successfully met all inclusion and exclusion criteria, the investigator or designee will call the central randomization number to obtain the assigned kit randomization numbers for that subject.

## **2.f Risks and Benefits**

The risks associated with warfarin are well known, and are primarily associated with bleeding events. Potential side effects include:

- Minor bleeding (nose bleeds, bleeding gums, bruising, bleeding from cuts that takes a long time to stop, heavier than normal menstrual bleeding)
- Allergic reactions
- Liver problems
- Low blood pressure
- Low red blood cells
- Paleness
- Fever
- Rash

Rare but serious side effects include:

- Death of skin tissue (skin necrosis or gangrene), purple toes syndrome
- Serious and life threatening bleeding problems. Signs or symptoms of serious bleeding problems, include:
  - Pain, swelling, or discomfort

- Headaches, dizziness, or weakness
- Unusual bruising (large bruises that grow in size)
- Nose bleeds that will not stop
- Pink or brown urine
- Red or black stools
- Coughing up blood
- Vomiting blood or material that looks like coffee grounds

There is some evidence that there may also be an increased risk of osteoporosis associated with the use of warfarin.(44)

Although a previous study has indicated that anticoagulation may provide a survival benefit to patients with IPF, it is uncertain that participation in this study will benefit an individual.(17) Participation in this study, however, may provide a better understanding of the efficacy of this treatment and may offer an improved therapy for future IPF patients.

### **2.g Early Withdrawal of Subjects**

Subjects may withdraw participation in the study at anytime. However, all subjects will be encouraged to remain in the study for the entire 48 week treatment period, even if it becomes necessary to withhold study agent.

Study drug discontinuation (either temporary or permanent) will be at the discretion of the study investigator in consultation with the subject's primary physician. Investigators should review all bleeding events (see section 9.b) for consideration of study agent withholding.

Subjects who have study agent withheld will be instructed to stop taking warfarin immediately and to continue monitoring their INR for one week. The DCC anticoagulation monitor will review the one-week INR value. If the value indicates that the subject is no longer anticoagulated, the monitor will confirm this with the coordinator. If the subject remains anticoagulated to any degree, the monitor will communicate to the coordinator that the subject should continue monitoring his or her INR for another week.

## **2.h When and How to Withdraw Subjects**

Subjects who are discontinued from study agent or who choose not to participate in study visits will be asked to return the INR monitoring equipment within 14 days of their discontinuation.

## **2.i Data Collection and Follow-up for Withdrawn Subjects**

Subjects who are withdrawn from study agent will be encouraged to remain in the study. Subjects who choose to withdraw from participation in the study will be asked to allow telephone follow-up by the coordinator for confirmation of survival.

## ***E3 Study Drug***

### **3.a Description**

Warfarin is an anticoagulant in the drug class of vitamin K antagonists. It is commonly used for the prevention of thrombosis and embolisms and has been approved for use in humans since 1954.

Warfarin is an oral agent and is available in tablets of several dosage levels.

In this study, these commercially available tablets will be overencapsulated according to cGMP standards. Matching placebo capsules will also be produced. Subjects will be provided with capsules at the 1mg and 2.5mg dosages. These capsules will be significantly different in both size and color to minimize any chance of subjects confusing dosages.

### **3.b Treatment Regimen**

At least weekly, subjects will monitor their INR, a measure of the level of anticoagulation. At each monitoring session, the subject will be given a weekly dosing regimen to ensure that the INR level remains between 2.0 and 3.0.

Because warfarin interacts with many substances, including other medications and certain foods, and because the metabolism of warfarin varies widely between subjects,

the dosing regimen for each subject may be unique and may change from week to week, depending on the conditions under which the drug is taken.

In cases where the therapeutic range is not met in consecutive measurements or where the subject's medications have been changed, the monitoring frequency of the INR will be increased to ensure that a stable range is achieved.

### **3.c Starting Dosage**

Subjects will be instructed to take 5 mg of warfarin or matched placebo at bedtime for the first three days. The investigator may choose a starting dose < 5 mg in cases where concomitant disease states / conditions (elderly patients, impaired nutrition, liver disease, congestive heart failure, patients who are at high risk of bleeding, or clinical judgment) or medications (eg, amiodarone), known to increase the sensitivity of warfarin exist. The next test will be scheduled for the morning of the fourth day. Subsequent dosing will be determined by INR response on the 4<sup>th</sup> day. The site coordinator will educate the subject on recording their warfarin dose in the study diary.

## **F Study Procedures**

### ***F1 Screening for Eligibility***

#### **1.a Diagnosis of IPF**

Only subjects with definite IPF will be eligible for enrollment in this study. We will utilize a combination of clinical/physiologic features, HRCT, and review of a clinically obtained surgical lung biopsy specimen to establish the diagnosis of IPF. An algorithm for the diagnosis is provided in the ACE-IPF MOOP to guide entry into the protocol as outlined in the inclusion and exclusion criteria. This multi-disciplinary approach uses expertise from clinicians, radiologists, and pathologists. Investigators at each site, in conjunction with central pathology, will work together to establish the diagnosis of IPF. This interactive approach to the diagnosis of IPF increases the level of agreement between observers.(45)

A subject with suspected ILD should be evaluated for secondary causes including, but not limited to, environmental exposures, drugs, and systemic diseases. Presence of any

of these findings felt to be significant enough to cause an ILD should disqualify the subject from entry into the trial.

If secondary causes are absent, an HRCT scan may be obtained. If an HRCT of sufficiently high quality has been obtained within the last 3 months, that scan may be used for diagnosis. In the appropriate clinical setting, the diagnosis of IPF can be made by the demonstration of a typical radiographic pattern on HRCT or by demonstration of UIP pattern on a surgical lung biopsy. The following criteria for a radiographic (ie, nonsurgical) diagnosis will be used. In the absence of known exposures and/or clinical associations attributable to pulmonary fibrosis, and in the appropriate clinical setting, the presence of definite UIP pattern in HRCT images is required to meet study criteria for the diagnosis of IPF.

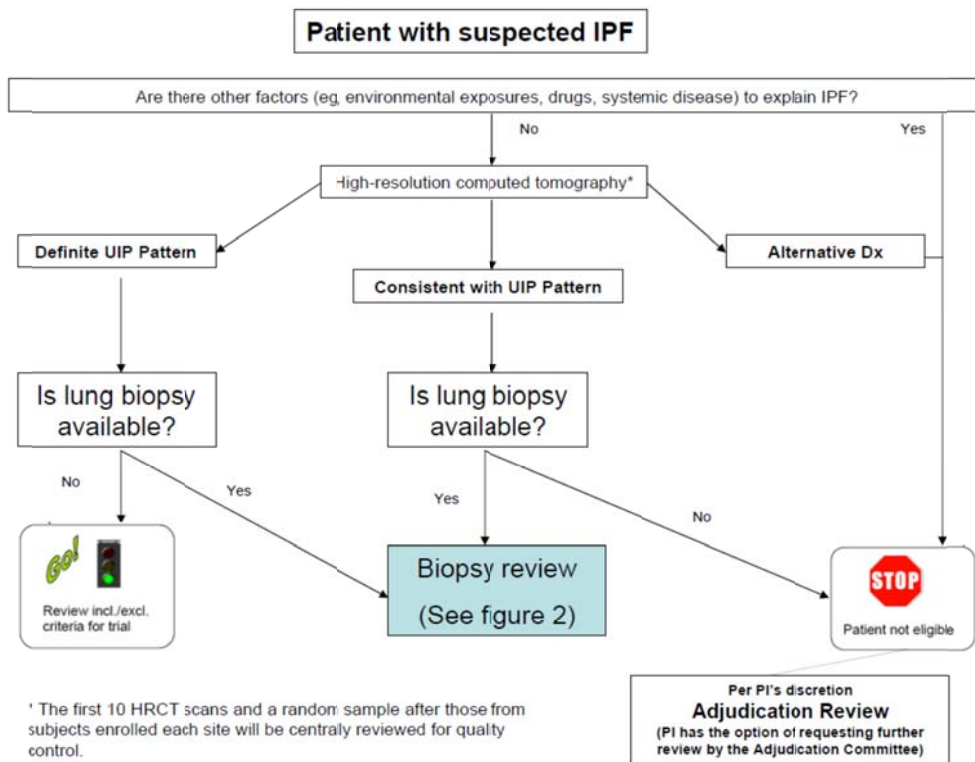


Figure 1: Diagnosis of Idiopathic Pulmonary Fibrosis in the IPFnet

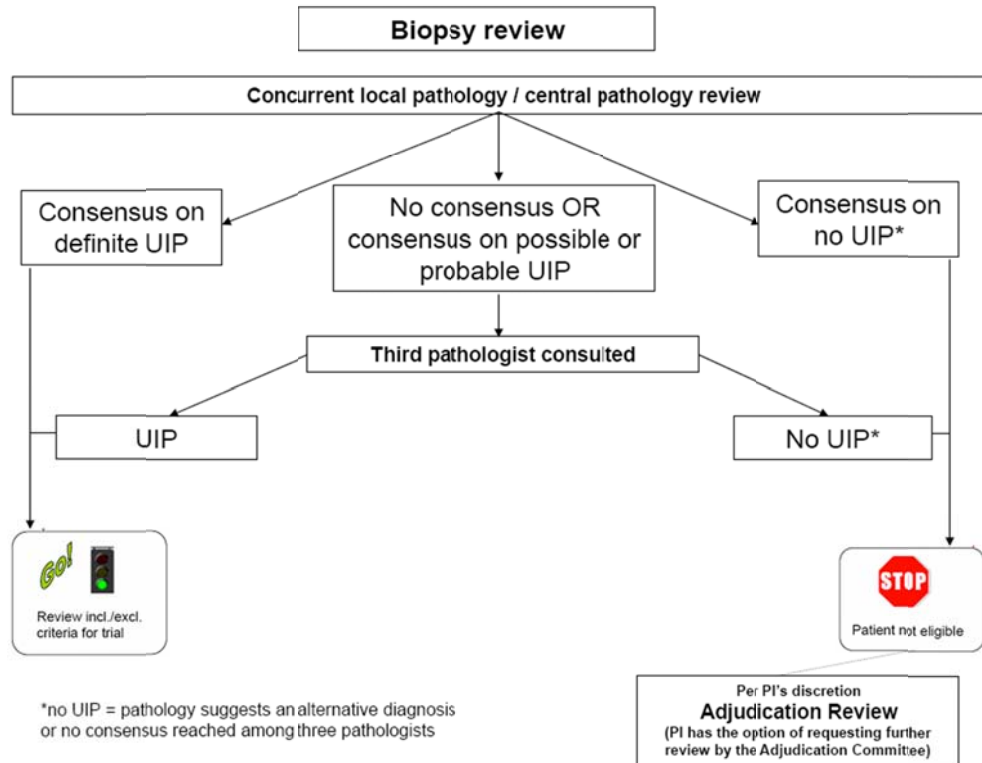


Figure 2: Pathology Flow Chart: Surgical Lung Biopsy Diagnosis

### Requirement for diagnosis

1. **Clinical:** exclusion of other known causes (connective tissue diseases, environmental and drug exposures) of ILD
2. **Radiographic:** HRCT with bibasilar reticular abnormality and honeycomb change with minimal ground glass opacities

### Appropriate clinical setting

1. Age > 50 years
2. Insidious onset of unexplained dyspnea
3. Duration of illness for  $\geq 3$  months
4. Bibasilar, inspiratory crackles

Unlike the ATS/ERS consensus criteria, bronchoscopy will not be required for diagnosis. This decision was made based on the experience of the IPFnet Steering Group



members regarding the utility of bronchoscopy in the diagnosis of IPF. The presence of an atypical HRCT finding will require documentation of a definitive diagnosis by surgical lung biopsy. If available, pathology data must be reviewed centrally to make a diagnosis of IPF.

We will not require central review of HRCT, as several studies have shown that a confident local interpretation of clinical/HRCT criteria as definite IPF/UIP is associated with a high positive predictive value for finding UIP at surgical lung biopsy (see Table 1). Differences in sensitivity in these series likely reflect subject selection, as Flaherty et al (46) evaluated only UIP and nonspecific interstitial pneumonia (NSIP), while Raghu et al (47) and Hunninghake et al (48) included a broader range of ILD.

**Table 1: Operating Characteristics of Local HRCT Review for Diagnosis of UIP**

Researcher	# of Subjects	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Raghu et al (Raghu 1999)	59 (29 UIP by SLB)	78	90	88	82
Hunninghake et al (Hunninghake 2003)	91 (54 UIP by SLB)	74	81	85	67
Flaherty et al (Flaherty, Thwaite, et al 2003)	96 (only NSIP & UIP)	37	100	100	30

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; UIP, usual interstitial pneumonia; SLB, surgical lung biopsy; and NSIP, nonspecific interstitial pneumonia.

Furthermore, an analysis of the HRCT scans from subjects enrolled in the GIPF-001 trial confirmed that local site interpretations have a high congruity to a central radiology core. In this multi-center study, 263 HRCT scans were read as definite IPF, and a retrospective central radiology core review found 93.2% to be consistent with IPF(49). We will also take several additional steps to insure that the local HRCT reads are accurate, including:

1. A detailed training module has been developed and must be completed by each site radiologist before site initiation.
2. Clinical centers are to mail all HRCT scans to the HRCT core lab. The first 10 HRCT scans from subjects enrolled at each enrolling site will be reviewed centrally to be certain that local reads are congruent with a central interpretation. If discrepancies are identified, additional education will be provided, and HRCT

scans will continue to be reviewed centrally until the central radiology core is confident that the local center is performing appropriately.

3. Random scans (after the first 10) from each center will be reviewed throughout the study to confirm that the local read continues to agree with central interpretation. If discrepancies are identified, they will be addressed as in #2 above.

In all cases, if a subject has a lung biopsy sample, that sample will be reviewed by the local and central pathologists. Therefore, the only cases that would not be subject to a direct central review process are those where the HRCT meets the centrally defined criteria for an unequivocal diagnosis and a lung biopsy sample is not available. Table 2 below summarizes the possible combinations for making a diagnosis.

**Table 2: Combining HRCT and Pathology Interpretations to Determine if IPF is Present**

HRCT Diagnosis	Pathology Diagnosis	Diagnosis of IPF
Definite UIP	Definite UIP	Yes
Definite UIP	Probable UIP	Yes
Definite UIP	Possible UIP	Yes
Definite UIP	Not UIP	No
Definite UIP	Unavailable	Yes
Consistent with UIP	Definite UIP	Yes
Consistent with UIP	Probable UIP	Yes
Consistent with UIP	Possible UIP	No
Consistent with UIP	Not UIP	No
Consistent with UIP	Unavailable	No
Inconsistent with UIP	Any path	No

Abbreviations: HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis;  
UIP, usual interstitial pneumonia; Dx, diagnosis

## **1.b Screening Procedures**

Once informed consent is obtained, subjects may immediately begin the screening process or may return within 28 days of consent. In the event a study subject has recently been clinically evaluated at the study site by an IPFnet study physician and has performed testing for this clinical evaluation that meets guidelines provided in the IPFnet or ACE-IPF Manual of Operating Procedures (MOOP). This testing may be used to satisfy the following screening criteria, if it was performed within 21 days of the screening visit: medical history, physical exam, arterial blood gas (ABG) with A-a gradient, vital signs with oximetry, body height and weight, spirometry, DLCO, lung volumes. An HRCT scan performed within 3 months of screening may be used, if of satisfactory diagnostic quality.

Allowing the use of previously performed test results that meet study guidelines for the screening visit is intended to permit subjects easier access to study entry, to prevent subjects from repeating testing that has been performed within the study window, and to decrease risks to subjects from repeated exposure to procedures such as arterial puncture and HRCT.

The following screening procedures will be performed:

- Medical history
- Physical exam (including pulse oxygen saturation)
- DLCO (adjusted for hemoglobin)
- Spirometry (post-bronchodilator)
- Lung volume
- Arterial blood gases (ABGs)
- HRCT (if not done in the last 3 months)
- Histopathologic review (if applicable)
- Collection of contact information, demographics, current therapies, and current symptoms
- Complete blood count

- Serum chemistry profile
- Urinalysis
- Electrocardiogram
- hCG (serum) pregnancy test (in women of childbearing potential)
- Assessment for known hypercoaguable states
- Finger-stick INR measurement with unencrypted INR monitor

All PFTs will be conducted by study personnel not directly involved in the treatment of the subjects. The DLco adjusted for hemoglobin will be used. The hemoglobin value will be obtained from the ABGs. If a second spirometry (FEV1 and FVC) are required per protocol (>21 days from screening) at enrollment visits this repeat spirometry will be used to determine baseline pulmonary function.

Subjects will be educated about the potential side effects of warfarin and the need for INR monitoring. They will be assessed to determine their ability and willingness to perform the necessary monitoring.

## **F2 Schedule of Measurements**

	Week															
	Screen	Enroll	1	4	8	12	16	20	24	28	32	36	40	44	48	54 <sup>1</sup>
Informed consent	X															
Medical history	X															
Physical exam (pulse oximetry)	X		X												X	
CBC and Chemistry	X	X	X				X				X				X	
Unencrypted INR measurement with site's INRatio Meter	X															
INR Test with Subject's Home INRatio Meter and Login to CoagCare		X														
Validate home monitor: INR test with Home INRatio Meter, communicate result to AM			X				X									
Validate home monitor: Lab INR measurement (venous)			X				X									
CBC and venous INR measurement <sup>3</sup>				X	X	X		X	X	X		X	X	X		
Urinalysis	X															
HRCT	X															
Lung Biopsy (if available)	X															
Serum pregnancy (if applicable)	X															
ECG	X															
6-minute walk test w/Borg scale		X													X	
Spirometry (post-bronchodilator)	X*	X*					X				X				X	X <sup>2</sup>
Diffusion capacity (DLCO)	X*	X*													X	
Lung volume measurement	X*	X*													X	
Arterial blood gases	X*	X*													X	
Quality of Life questionnaires		X					X				X				X	

Gender Substudy Questionnaire		X													
Biological response blood draw (D-dimer)		X				X									
Research blood draws (if consent given)		X				X			X					X	
Evaluate for acute exacerbations			X			X			X					X	
Review adverse events			X			X			X					X	X
Review concomitant meds	X	X	X			X			X					X	
Dispense subject diary		X	X			X			X						
Review subject diary			X			X			X					X	
Dispense study treatment		X				X			X						

\* This test must be completed no more than 21 days prior to the enrollment visit, or else it must be repeated at enrollment.

<sup>1</sup> This visit will occur at the site only if required for FVC confirmation (see section F7); otherwise this will be a telephone follow-up.

<sup>2</sup> Measurement performed only if the visit is at the site and confirmatory FVC measurement is required.

<sup>3</sup> These lab draws may occur at the clinical site or a local lab draw station, depending on subject preference.

Subjects will be contacted by a study coordinator at least once each month that the subject does not have a scheduled visit to the clinical center.

## 2.a Biological sample collection and management

Subjects who consent to having blood drawn for storage in the bio-repository for the banking of blood, blood components, and other biologic specimens (urine and bronchoalveolar lavage fluid) will have approximately 40.5 mL of blood drawn, 17 mL blood drawn for DNA and 20 mL of urine collected at enrollment visit. Subjects will have approximately 50 mL of blood drawn and 20 mL urine specimen collected at each 16-week follow up visit. During suspected AEx (as defined in the ACE-IPF MOOP) subjects will have approximately 35 mL of blood drawn for research purposes and other clinically obtained biologic specimens (BAL) that would otherwise be discarded will be collected whenever possible.

Subjects will be given an AEx kit to carry with them to the hospital or doctor's office when they have an episode of suspected AEx. The kit will include tubes to collect blood. If a subject presents to their local clinical center with a suspected AEx in addition to collecting blood we will collect other biologic specimens (BAL) collected from clinically performed procedures (specimens that would otherwise be discarded).

Blood specimens will be separated according to ACE-IPF MOOP guidelines into the following components for banking in the repository; serum, plasma and DNA. Coding of

all biologic-specimens for the repository will be performed by study staff at the clinical center. The samples will be processed per ACE-IPF MOOP guidelines, aliquoted, labeled with barcode labels, and stored at -70°C at the clinical center. At regular intervals, samples will be batched and shipped to the central repository.

The central repository will be managed by NHLBI. The NHLBI sets up a contract with a company that can perform repository functions for NHLBI trials. IPFnet has been granted permission to utilize this resource.

Samples shipped to the NHLBI repository will be labeled with barcode labels, no demographic information or subject identifiers will be included on the label. The only identifier will be a sample ID. This sample ID will be linked in the DCC clinical database to subject information. No subject information will be transferred to the biological specimen database.

The subject's samples may be utilized for approved substudies relating to human disease, including, but not limited to, IPF. The studies for which an individual's samples will be made available will be determined by the subject's answers to questions on the biological sample informed consent form. The subjects can choose to make their samples available for all options or any combination. Samples will be made available to researchers only with IPFnet Steering Group approval until such time as the samples are made public through the NHLBI repository.

## **2.b Biological response (D-dimer) blood collection**

At the enrollment visit and week 16, blood will be drawn for the measurement of D-dimer levels. These measurements will allow the determination of the subject's reaction to the anticoagulant by comparing the D-dimer levels prior to therapy (enrollment) and after a stable INR has been reached (week 16.) This measurement is conducted by the central laboratory and collection materials will be included in the site's laboratory kits for those visits.

### **2.c INR meter validation (Venous INR blood collection)**

At week 1 and week 16 a venous INR measurement will be performed. The INR measurement will be performed by the central laboratory and collection materials will be included in the site's laboratory kits for those visits.

Within an hour of the venous INR blood draw, the subject should conduct an INR measurement with the encrypted INR monitor they were provided at enrollment. This requires that the subjects bring the INR monitor to their week 1 and week 16 site visits. The INR code provided by the encrypted meter should be communicated to the DCC Anticoagulation Monitor by the study coordinator.

### **2.d Interim Safety Monitoring**

Subjects will have blood drawn for safety monitoring (including complete blood counts and PT / INR testing) once a month, including all study visits. Safety monitoring outside of the normal study visits will occur at:

- Week 4
- Week 8
- Week 12
- Week 20
- Week 24
- Week 28
- Week 36
- Week 40
- Week 44

Subjects will either return to the clinical center or visit a local blood draw station associated with the study central laboratory. The closest location for each subject will be determined by the study coordinator at the enrollment visit.

At each study visit, subjects will be provided requisition forms for the required safety testing. These forms must be brought to each blood draw appointment, whether they occur at the clinical center or a local draw station.

The results of these tests will be sent from the lab to the IPFnet DCC Anticoagulation Monitor. Upon receipt, the Anticoagulation Monitor will provide the clinical center coordinator with a copy of the blood count test results. The coordinator and investigator should compare these results against previous test results to ensure that there is no indication of anemia or hemorrhage. If withdrawal from study agent is clinically indicated, see section E2.g for further instruction.

### ***F3 Enrollment Visit***

If the subject has met all entrance criteria for participation in the study, he or she will return for an enrollment visit.

During this visit, the following procedures will occur:

- Subjects will perform the 6MWT.
- Subjects will complete quality of life (QOL) questionnaires.
- Subjects will complete the Gender substudy questionnaire if applicable
- Subjects will receive training on the home INR monitoring.
- Subjects will be randomized into the trial.
- Subjects will be provided with the necessary equipment for home monitoring of their INR.
- Subjects will perform first login to CoagCare (ace-ipf.net) using their individual account, will perform an INR test using their encrypted meter, and will enter this result into CoagCare.
- Subjects will receive a diary and will receive sufficient study agent to last until their week 16 visit.
- Blood for CBC, chemistry panel, and INR measurement will be drawn.
- Blood for measurement of biological response (D-dimer) will be drawn.
- If consent has been given, a research blood draw will occur.
- If the following tests were performed for screening more than 21 days prior to the enrollment visit, they must be repeated at this visit:
  - a. Post-bronchodilator spirometry test



- b. DLCO (adjusted for hemoglobin)
- c. Arterial blood gas
- d. Lung volumes

#### ***F4 Week 1 Visit***

The week-1 visit may occur between 1 and 2 weeks after enrollment. The goal of this visit is to verify that the subject is experiencing no negative effects from the study drug, the subject understands the home monitoring system and is able to use it properly, and the subject is managing the study drug dosage. Also at week 1, the home INR monitor is validated by checking a venous PT/INR and a home monitor PT/INR within one hour of each other.

During this visit, the subject will:

- have a physical examination
- have blood drawn for CBC, chemistry panel, and INR measurement ,
- meet with the study coordinator to
  - review concomitant medications,
  - evaluate for adverse events and acute exacerbations,
  - review the monitoring system and drug dosing,
  - conduct an INR measurement on the subject's encrypted INR meter, and
  - review the subject's patient diary.

No additional study drug will be dispensed during this visit.

#### ***F5 Week 16 and 32 Visits***

These visits may occur +/- 2 weeks from their scheduled date. The purpose of these visits is to collect the subject's pulmonary function values.

During these visits, subjects will:

- undergo a post-bronchodilator spirometry test,
- have blood drawn for CBC and chemistry panel,
- complete QOL questionnaires,

- meet with the study coordinator to:
  - review concomitant medications,
  - evaluate for adverse events and acute exacerbations,
  - review the home monitoring system and drug dosing,
  - provide additional INR testing supplies (if necessary),
  - review the subject's patient diary, and
  - collect unused study agent.

At week 16, blood will be drawn for measurement of D-dimer and to validate the INR home monitor (validation involves a finger stick and a venous PT/INR)

If consent has been given, a research blood draw will occur.

At these visits, sufficient dosage will be dispensed to last until the next scheduled study visit.

## ***F6      Week 48 Visit***

The week 48 visit may occur +/- 2 weeks from the scheduled date. The purpose of this visit is to collect the subject's pulmonary function values, along with secondary endpoint values and key safety information.

During these visits, subjects will:

- undergo a physical examination,
- have blood drawn for a CBC / chemistry panel,
- have an ABG measurement,
- perform a post-bronchodilator spirometry test,
- have a DLCO measurement (adjusted for hemoglobin),
- have a lung volume measurement,
- perform a 6MWT,
- complete QOL questionnaires,
- meet with the coordinator to
  - review concomitant medications,
  - evaluate for adverse events and acute exacerbations,

- review the subject's patient diary, and
- collect unused study agent, computer and data access card (if provided)..

Patients should retain their INR monitor to complete the final anticoagulation evaluation (see section 9.a.) and be provided with shipping materials for return of the monitor upon confirmation that the anticoagulation effect has ended.

If consent has been given, a research blood draw will occur.

### ***F7 Week 54 Visit***

At week 54, all patients need a safety evaluation and identification of adverse events. In most cases, this can be performed with a telephone follow-up. An on-site visit will be required for subjects who require an FVC confirmation because:

- 1) They had not reached the hospitalization component of the primary endpoint, and
- 2) They had a measured drop of FVC of >10% from baseline on their previous site visit, and
- 3) They had not previously had a confirmed FVC drop of >10% from baseline.

During a telephone follow-up, subjects will be evaluated for adverse events.

During an on-site visit, subjects will complete a spirometry test and be evaluated for adverse events.

### ***F8 Long term mortality follow up***

During the consenting process, patients will be asked for permission to allow the DCC to follow-up on mortality at the end of the study. Subjects who have consented to this will have their survival status checked through the National Death Index at the time the ACE-IPF study concludes.

## **F9     *INR Monitoring and Bleeding Events***

### **9.a     Safety and Compliance Monitoring**

Each subject will have access to an encrypted INR meter and an FDA-cleared web-based warfarin management system (WMS). If the subject has access to a computer and the internet, subjects should access the WMS directly and answer all questions and provide the encrypted INR value. In cases where internet access is unavailable to a subject, this information will be communicated by telephone to the DCC anticoagulation monitor, who will enter the information on behalf of the subject and convey the WMS' dosage adjustment and testing instructions to the subject. Subjects and coordinators will be unable to see INR values in the WMS and will, therefore, remain blinded to treatment.

The DCC anticoagulation monitor, a clinical pharmacist with experience in anticoagulation management, will oversee the automated dosing management system. The monitor will review each set of dosage instructions given to a subject. In the event that the monitor disagrees with the prescribed dosing regimen, the monitor will, in consultation with an MD, generate appropriate instructions and communicate them to the site and patient.

Subjects will be expected to monitor their INR values at least once per week. These values will be decrypted and a dosing schedule for the following week will be provided to the subject

Information relating to adverse, drug-related symptoms will be collected at each weekly measurement, along with any changes to medications or diet. These data will be used to modify, if necessary, the subject's dosing schedule.

If the subject has experienced any potentially drug-related symptoms, has had multiple consecutive non-therapeutic INR values, or has changed medications that could interact with warfarin, then s/he will be instructed accordingly (e.g. contact medical personnel if the symptoms warrant) and will be expected to re-check the INR within 3 days to ensure that a therapeutic range is reached and maintained.

If a subject does not adhere to a regular INR monitoring schedule, the subject's study coordinator will be notified and instructed to contact the subject to determine why no monitoring is taking place.

Once a subject stops taking study agent, they should no longer monitor their INR through the CoagCare system. Subjects will be asked to monitor their INR at least once after the final dose of study drug is taken, in order to ensure that the anticoagulation effect has ceased. This monitoring activity will be done by contacting the DCC Anticoagulation Monitor directly. The DCC anticoagulation monitor will review the INR value and if the value indicates that the subject is no longer anticoagulated, the monitor will inform the subject and confirm this with the coordinator. The subject will be asked to return the INR monitor and any unused testing materials to the study coordinator.

If the subject is still anticoagulated to any degree, the monitor will communicate to the subject and coordinator that the subject should continue monitoring his or her INR for another week.

Once a subject is no longer anticoagulated, all testing materials provided should be returned to the study coordinator.

Study coordinators will contact subjects by telephone in any month that a clinic visit does not occur to ensure the subject has no difficulties with the monitoring system and that the subject has an adequate supply of study drug.

### **9.b Definition of Bleeding Events**

Bleeding Events will be categorized as either major or minor and will be evaluated by the criteria below for both severity and consideration of discontinuation of study drug:

#### **Major Bleeding**

1. Fatal bleeding OR
2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular resulting in vision changes, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome OR

3. Bleeding causing a decrease in hemoglobin level of 2 g/dl or more and/or
4. Bleeding leading to transfusion of 2 or more units of whole blood or red blood cells (50, 51)

### **Minor Bleeding**

1. Bleeding which does not meet Major Bleeding status but prompts the subject to seek medical attention

In the event of Major Bleeding events, the subject should undergo evaluation for study agent discontinuation as outlined in section E.2.g.

The IPFnet Adjudication Committee will review all clinical information to make the final determination for minor / major bleeds.

## ***F10 Safety and Adverse Events***

### **10.a Definitions of Adverse Events**

An adverse event (AE) is any untoward medical occurrence in a clinical-investigation subject administered a pharmaceutical product. An AE does not necessarily have a causal relationship with this study drug. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered to be related to the medicinal product. Diseases, signs, symptoms, or laboratory abnormalities already existing at enrollment are not considered AEs unless they worsen (i.e., increase in intensity or frequency). Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Surgical procedures planned prior to randomization and the conditions leading to these measures are not AEs.

A serious adverse event is any untoward event that:

- is fatal
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization, with the following exceptions:

- Preplanned (prior to the study) hospital admissions unless the hospitalization is prolonged
- Planned admissions (as part of a study, e.g., routine biopsies)
- 23-hour rehospitalizations
- Hospitalization for elective procedure
- Emergency room visits
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- important medical events that may not result in death, be life-threatening, or require inpatient hospitalization may be considered an SAE when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Life-threatening means that the subject was, in the view of the investigator, at immediate risk of death from the AE as it occurred. It does not include an AE that, had it occurred in a more severe form, might have caused death.

Persistent or significant disability/incapacity means that the event resulted in permanent or significant and substantial disruption of the subject's ability to carry out normal life functions.

Associated with the use of the drug means that there is a reasonable possibility that the experience may have been caused by the drug.

### **10.b Data Collection Procedures for Adverse Events**

For the IPFnet ACE-IPF trial, all AEs (serious and nonserious) will be recorded from randomization through final study visit on the AE CRF. All SAEs will be recorded from randomization through 28 days after discontinuation of study drug.

### **10.c Reporting Procedures**

Regardless of causality, the investigator must complete and submit an SAE eform to the DCRI Safety Surveillance within 24 hours of knowledge of the event for all serious adverse events occurring from Randomization through the Safety Telephone Follow-Up.

When additional relevant information (final diagnosis, outcome, results of specific investigations, etc.) becomes available, the investigator must record follow-up information in the electronic database. Follow-up information should be recorded according to the same process used for reporting the initial event as described above. The investigator will follow all reportable events until resolution or stabilization. For questions concerning reportable events please contact:

DCRI Safety Surveillance

Telephone: (919) 668-8624 or (866) 688-7799 (toll free)

DCRI Safety Surveillance will follow all SAEs until resolution, stabilization, or until the last patient completes the Safety Telephone Follow-Up, whichever occurs first. DCRI Safety Surveillance will report any death and study drug-related SAEs to the NHLBI designee and DSMB within 1 business day. All other SAEs will be reported within 1-2 days of receipt to the NHLBI and DSMB.

Any serious adverse event that is ongoing when a patient completes his/her participation in the trial must be followed by the site investigator until any of the following occurs:

- The event resolves or stabilizes.
- The event returns to baseline condition or value (if a baseline value is available).

For events ongoing at the time the clinical database is closed, DCRI Safety Surveillance will notify the NHLBI and record these events as unresolved.

AEs that meet the criteria of serious, study drug-related, and unexpected per the U.S. package insert, qualify for expedited reporting to the regulatory authorities. The DCRI Safety Surveillance Medical Monitor will perform a medical review of all deaths and study drug-related SAEs submitted and evaluate for “unexpectedness.” DCRI Safety Surveillance will notify the site if the event is determined to be “unexpected”. Site investigators are required to complete and submit the voluntary form 3500 MedWatch online for the events identified as serious, drug-related, and unexpected at <https://www.accessdata.fda.gov/scripts/medwatch/>.



### **10.d DSMB Reporting Period**

The DSMB will review collected study data related to safety and efficacy as scheduled in the DSMB charter. At each review the DSMB will provide written comments to the NHLBI about any concerns the Board may have regarding safety, feasibility, or benefit of continuing the study.

The DSMB will also receive information regarding any serious adverse events within 2 business days of the DCC's receipt of such information from the clinical site.

### **10.e Unblinding Procedures**

The DCC Medical Monitor will be available to the study physician to help consider the need for unblinding on a case-by-case basis. Unblinding will be permitted ONLY for subject safety. Specifically, the blind should be broken only for serious, unexpected, and drug-related AEs or when required by local regulatory authorities, when the knowledge of treatment assignment is needed for subject safety. The clinical center investigator must notify the DCC before unblinding any subject. The clinical center investigator must notify the DCC Medical Monitor at the DCC to begin the unblinding process for any subject. In an emergency, if the clinical center investigator is not immediately available, the attending physician may contact the DCC Medical Monitor directly. Emergency contact wallet cards will be provided to all study subjects.

Contact Information for DCC Medical Monitor(s):

Pager number: 919-970-7435

## **G Statistical Plan**

### **G1 Sample Size Determination and Power**

This placebo-controlled, double-blind, randomized trial will evaluate the benefits and risks of home-monitored warfarin therapy in a rigorously defined IPF population.

Subjects will be randomized to warfarin vs. placebo therapy in a 1:1 fashion. The trial is designed with the intention of following every subject for 48 weeks. In table G.1, we present the required number of events for a time-to-event trial with Type I error rate of 0.05 and a 1:1 randomization ratio.(52) Based on input from the IPFnet Steering Group, the study is designed to have 90% power to detect a difference in 48-week event-free rates of 70% for the warfarin group vs. 50% for the placebo group. This trial will need to have at least 95 primary adjudicated endpoints to achieve 90% power. It is expected that some events will be in the adjudication process at the time the study end date is established.

**Table G.1. Required Number of Events and Sample Size**

<b>Event-Free Rate (Warfarin Group)</b>	<b>Event-Free Rate (Placebo Group)</b>	<b>Number of Required Event</b>	<b>Total Sample Size (85% Power)</b>
0.70	0.50	95	256
0.70	0.45	65	170
0.75	0.55	79	246
0.75	0.60	127	416
0.70	0.55	158	440

The primary endpoint for the study is a time-to-event variable with three components: death, non-elective, non-bleeding hospitalization, and a greater than or equal to 10% absolute drop in FVC from the baseline assessment. Data from a cohort of IPFnet subjects with characteristics fitting the inclusion criteria for the ACE-IPF trial were used to estimate event rates needed to determine the sample size. From the recently published STEP-IPF trial, we observed a 24-week pooled event rate of 31.0% for all-cause death or hospitalization.(53) Furthermore, we observed a 24-week pooled event

rate of 51.6% for the composite endpoint of mortality, acute exacerbation, hospitalization, or 10% drop in FVC (liters) from baseline.

These estimates were based on the 180 STEP-IPF subjects who were followed for a total of 24 weeks. It is expected that the ACE-IPF population will be slightly lower risk than the STEP-IPF population. However with the addition of the FVC decline component, we expect 48-week event-free rates of 50% for placebo subjects for the primary endpoint.

From the Kubo et.al. (2005) data, we have hypothesized 48-week event-free rate of 70% in the warfarin therapy arm for the sample size calculations. Based on these assumptions we would need to enroll 256 patients to achieve 90% power.

#### **Power Analysis for Secondary Endpoints**

Power calculations for secondary endpoint measurements are shown in Table G.2. Standard deviations are based on data from the STEP-IPF subjects. The calculations are based on a 2-sample t-test with Type I error rate set at 0.05 and 85% power. These calculations are likely to be conservative because the statistical approach for analyzing these endpoints will incorporate incomplete observations as well as intermediate data points. These calculations factor in the assumption that between 10 and 20% of subjects will not survive to the 48 week visit.

**Table G.2: Detectable Differences for Selected Endpoint Measurements**

<b>Secondary Endpoints</b>	<b>Std Dev of the Baseline Score</b>	<b>Detectable Difference for n=200</b>	<b>Detectable Difference for n=230</b>
<b>FVC (% predicted)</b>	14.0	6.0	5.6
<b>DLCO (% predicted)</b>	6.0	2.6	2.4
<b>6MWT Distance Walked (meters)</b>	115	49.0	45.6

Abbreviations: Std Dev, standard deviation; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide; 6MWT

## ***G2 Interim Monitoring and Early Stopping***

The IPFnet Data Safety and Monitoring Board (DSMB) will review subject safety and trial conduct at periodic points during the study. The DSMB may require analyses of the primary endpoint results for weighting the benefits and risks of the treatment strategies. Because the DSMB can stop the trial for safety concerns or for a large efficacy benefit, there will be multiple opportunities to reject the null hypothesis (no difference in event rates between the placebo and active groups). Without adjusting the levels for the repeat-testing environment, the probability of making a type I error can be greatly inflated over the nominal 0.05 level for the warfarin vs. placebo comparison. The O'Brien-Fleming Spending Function for group sequential monitoring will be used with planned assessment of the primary endpoint approximately once per year. These evaluations will include an assessment of conditional power. For the endpoint of all-cause mortality, the Haybittle-Peto boundary, which requires  $P < .001$  as evidence required to consider stopping a trial early for benefit or harm will be applied.

The two key outcomes for DSMB review are the rates of all-cause mortality and major bleeding across study groups. The DCC will prepare the following documents for the IPFnet DSMB to review:

- SAE forms with real-time clinical narratives sent via password-protected email within 1-2 business day of receipt
- Regular summaries of SAEs reported on a periodic basis
- Detailed summaries of all SAEs and AEs reported at 6-month intervals

## ***G3 Analysis Plan***

Before locking the database, the statistical analysis plan (SAP) will undergo final validation and will provide complete details on the statistical analysis. Before data analysis, the SAP will be approved by the IPFnet Steering Group and the IPFnet DSMB. All analyses will be based on intent-to-treat principles using all randomized participants.

Baseline factors across groups will be compared using mean (standard deviation) and median (25th and 75th percentiles) summary measures. Kaplan-Meier curves will be used to display event rates. Due to clinical interest in departures from both sides of the null hypothesis, all test statistics will be 2-sided. We will take a conservative approach with respect to the analysis of subgroups – both planned and unplanned. For subgroup analyses, a conservative significance level of 0.01 will be used for all interaction tests. Plots will be used to assess the consistency of response across key subgroups. The trial results will be reported according to guidelines specified in the CONSORT statement.<sup>(54)</sup> A flow diagram describing screening, recruitment, randomization, dropout, and vital status will be included in the primary manuscript. AEs and efficacy data will be presented by the treatment groups. Adherence, dropout, and lost to follow-up will be carefully examined across the treatment groups. Analyses of safety will be based on data from all randomized subjects who received at least 1 dose of study drug.

#### **G4     *Statistical Methods***

The primary hypothesis will be tested using a Cox proportional hazards model comparing the treatment effect on the time-to-event outcome of death, 10+% absolute drop in FVC from baseline, and non-elective, non-bleeding hospitalization. Covariates in this model will include an indicator variable for the treatment group and the DLCO measurement from the screening assessment. The treatment effect will be summarized using the estimated hazard ratio and the 95% confidence interval. For continuous outcomes measured over time, a mixed model repeated measures (MMRM) analysis will be used to describe patterns of response for the treatment groups.<sup>(55)</sup> Regression modeling approaches using either the logistic regression model or Cox proportional hazards regression model will be employed when appropriate. The validity of these models will be assessed via standard modeling diagnostics and goodness-of-fit measures. Estimates of cumulative frequencies for more general time-lagged responses such as medical costs and resource utilization will be calculated using the partitioned version of the Bang-Tsiatis estimator.<sup>(56)</sup> The partitions will be set at 16-week intervals to correspond with the data-collection process. Covariate adjusted event rates will be calculated using inverse probability-weighted regression estimates.<sup>(57)</sup>

## **G5    *Missing Outcome Data***

To reduce the amount of missing data, subjects will be encouraged to return for all study visits even after experiencing a non-fatal primary event. Assuming that data are missing at random, the statistical methods described earlier including the Cox proportional hazards models, the MMRM models, and the IPW methods provide valid estimates without the need to impute data.

# **H Data Handling and Record Keeping**

## **H1    *Confidentiality and Security***

Access to databases will be controlled centrally by the DCC 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. Oracle has many security features to ensure that any staff member accessing the database has the proper authority to perform the functions he or she requests of the system. Within the secondary SAS databases, UNIX group-access control maintains similar security. The Sun workstation login is secured by extensive user-password facilities under UNIX.

Database back-up will be performed automatically every day, and standard IPFnet DCC policies and procedures will be applied to dictate tape rotation and retention practices.

All disk drives that provide network services, and all user computers, will be protected using virus-scanning software. Standard IPFnet DCC policies will be applied to update these protection systems periodically through the study.

## **H2    *Training***

The training plan for clinical center staff includes provisions for training on assessments, eCRF completion guidelines, data management procedures, and the use of computerized systems. Training will occur prior to the beginning of the study.

### ***H3 Case Report Forms and Source Documents***

#### **3.a Design and Development**

The IPFnet 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. The remainder of this section provides an overview of the data management plan associated with this protocol.

#### **3.b Data Collection Forms**

The data collection process consists of direct data entry at the study clinical centers into the EDC system(s) provided by the DCC. A backup paper CRF will be provided to clinical centers for recording data in the event the EDC system is unavailable. Data entry of the eCRFs 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 eCRFs for each research participant.

#### **3.c Data acquisition and Entry**

Data entry into electronic CRFs 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.

#### **3.d Data Center Responsibilities**

The IPFnet DCC will 1) develop a data management plan and will conduct data management activities, 2) provide final eCRFs for the collection of all data required by the study, 3) develop data dictionaries for each eCRF that will comprehensively define each data element, 4) conduct ongoing data monitoring activities on study data, 5)

monitor any preliminary analysis data clean up activities, and 6) rigorously monitor final study data clean up.

### **3.e Data Editing**

Completed data will be entered into the IPFnet DCC automated data acquisition and management 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 the IPFnet DCC automated data acquisition and management system.

## ***H4 Records Retention***

Copies of collected information will be retained as dictated by DCRI Standard Operating Procedures.

# **I Study Monitoring, Auditing, and Inspecting**

## ***I1 Study Monitoring Plan***

The IPFnet DCC or its designees will monitor the study progress, as frequently as is necessary to assure compliance with applicable Good Clinical Practices, FDA and NIH regulations and protocol procedures and to monitor completion of CRFs. Arrangements for monitoring visits will be agreed to in advance of planned visits, except in the case of an emergency. FDA or other health authority representatives reserve the right to visit clinical centers at any time.

# **J Study Administration**

## ***J1 Organization and Participating Centers***

The administrative and funding mechanism used to undertake this project is a “Cooperative Agreement” (U01), which is an assistance mechanism. Under the cooperative agreement, the NHLBI assists, supports, and/or stimulates the study and is



substantially involved with investigators in conducting the study by facilitating performance of the effort in a “partner” role. The NHLBI Project Scientist serves on the Steering Group, and he or another NHLBI scientist may serve on other project committees, when appropriate. At the same time, however, NHLBI does not assume a dominant role, direction, or prime responsibility for this research program.

As described below, governance of the project is conducted through a steering group. PIs have lead responsibilities in all aspects of their trials and the project, including any modification of trial designs, conduct of the trials, quality control, data analysis and interpretation, preparation of publications, and collaboration with other investigators, unless otherwise provided for by the Steering Group.

PIs retain custody of and have primary rights to their center-specific and collaborative data, subject to government rights-of-access consistent with current Health & Human Services (HHS), Public Health Service (PHS), and NIH policies. The protocols and governance policies call for the continual submission of data centrally to the DCC for the collaborative database. At a minimum, the database will contain the key variables selected by the Steering Group for standardization across all clinical centers; procedures for data analysis, reporting, and publication; and procedures to protect and ensure the privacy of medical and genetic data and records of individuals. The NHLBI Project Scientist, on behalf of the NHLBI, will have the same access, privileges, and responsibilities regarding the collaborative data as the other members of the Steering Group.

PIs are also encouraged to publish and to publicly release and disseminate results, data, and other products of the project, concordant with the project protocols and governance and the approved plan for making data and materials available to the scientific community and to the NHLBI. However, during or within 3 years beyond the end date of the project period of NHLBI support, unpublished data, unpublished results, data sets not previously released, or other study materials or products are to be made available to any third party only with the approval of the Steering Group.

Upon completion of the project, PIs are expected to put their intervention materials and procedure manuals into the public domain and/or make them available to other

investigators, according to the approved plan for making data and materials available to the scientific community and the NHLBI for the conduct of research, at no charge other than the costs of reproduction and distribution.

The NHLBI reserves the right to terminate or curtail the project (or an individual award) in the event of (a) failure to develop or implement mutually agreeable collaborative measurement, participant eligibility, and data management sections of the protocols; (b) substantial shortfall in subject recruitment, follow-up, data reporting, quality control, or other major breach of protocol; (c) substantive changes in the agreed-upon protocols with which NHLBI cannot concur, (d) reaching a major project outcome substantially before schedule with persuasive statistical significance, or (e) human subject ethical issues that may dictate a premature termination.

Any disagreement that may arise in scientific/programmatic matters (within the scope of the award) between award recipients and the NHLBI may be brought to arbitration. An arbitration panel will be composed of 3 members—1 selected by the Steering Group (with the NHLBI member not voting) or by the individual PI in the event of an individual disagreement; a second member selected by NHLBI; and the third member selected by the other 2 members. This special arbitration procedure in no way affects the PI's right to appeal an adverse action that is otherwise appealable in accordance with the PHS regulations at 42 CFR part 50, Subpart D, and HHS regulation at 45 CFR part 16 or the rights of NHLBI under applicable statutes, regulations, and terms of the award.

## ***J2 Funding Source and Conflicts of Interest***

The funding for this study comes from grants to IPFnet clinical centers and to the IPFnet DCC.

## ***J3 Committees***

The IPFnet has several active committees that are responsible for the development and oversight of this study, including:

- Steering Committee
- Performance Committee
- Measurements & Endpoints Committee

- Publications Committee
- Conflict of Interest Committee

This protocol has been reviewed and approved by an independent Protocol Review Committee (PRC) and by an independent Data and Safety Monitoring Board (DSMB).

The DSMB will review the data collected in this study on a regular basis to ensure data quality and participant safety and to provide independent advice to the NHLBI regarding progress and the appropriateness of study continuation.

#### ***J4 Subject Stipends or Payments***

Subjects will not be paid for their participation in this study. Subjects will receive reimbursement for their travel expenses.

Subjects will also receive, at the time of enrollment, a home INR monitor. Subjects may also receive a laptop computer, data access card, and an internet access plan while the subject is active in the study. These are intended solely to facilitate safety monitoring and will be returned once participation in the study is complete.

#### ***J5 Study Timetable***

It is anticipated that enrollment for this study will be complete in the fall of 2011. Study follow-up will be complete 54 weeks after enrollment.

## **K Investigator Agreement**

I have read the foregoing protocol, ACE-IPF, and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the study.

I will fulfill all responsibilities for submitting pertinent information to the local IRB, if applicable, that is responsible for this study.

I further agree that NHLBI and/or DCRI will have access to any source documents from which eCRF information may have been generated.

\_\_\_\_\_  
Signature of Principal Investigator

\_\_\_\_\_  
Date

\_\_\_\_\_  
Name of Principal Investigator (printed or typed)

Protocol version date: July 21, 2009

Amendment 1 date: June 14, 2010

Amendment 2 date: October 19, 2010

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