STUDY OF THERAPEUTIC PLASMA EXCHANGE, RITUXIMAB, AND INTRAVENOUS IMMUNOGLOBULIN FOR ACUTE EXACERBATIONS OF IDIOPATHIC PULMONARY FIBROSIS

(STRIVE-IPF)

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PROTOCOL SYNOPSIS

Protocol Title:	**Study of Therapeutic Plasma Exchange, Rituximab, and Intravenous Immunoglobulin for Acute Exacerbations of Idiopathic Pulmonary Fibrosis (STRIVE-IPF)**
Protocol Number:	UAB OSP#: 000513913
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Participating Medical Centers:	1. University of Alabama at Birmingham (UAB) 2. Brigham and Women's Hospital (BWH) (No Longer Active) 3. Temple University Hospital (TUH) 4. University of Pittsburgh Medical Center (UPMC) 5. Baylor University Medical Center 6. University of Utah Medical Center 7. Thomas Jefferson Medical Center
UAB Data Coordinating Center:	Rahman Fazlur Ph.D., Director
Sponsor:	National Heart, Lung, and Blood Institute (UO1HL133232)
Study Rationale:	The experimental therapy here, mechanistically targeted to ameliorate autoantibody-mediated pulmonary injury, seems to result during pilot studies in significant benefit for a disease syndrome that has, until now, been almost invariably inexorable. This clinical trial has the potential to profoundly affect current paradigms and treatment approaches to patients with acute exacerbations of IPF (AE-IPF).
Study Objectives:	The primary goal of clinical trial is to determine effects of combined therapeutic plasma exchange (TPE), rituximab, and intravenous immunoglobulin (IVIG) in comparison to effects of treatment as usual (TAU), among AE-IPF patients.
Study Hypothesis:	Our central hypothesis is "***AUTOANTIBODY REDUCTION IS BENEFICIAL FOR AE-IPF PATIENTS."*** A corollary of this hypothesis is that antibody-mediated autoimmunity can play an important role in IPF exacerbations.
Study Aims:	1. To conduct a mechanistically-driven trial to examine effects of autoantibody reductive treatments on the 6 month survival of patients with acute exacerbations of IPF. 2. To determine the effects of the experimental treatment (TPE+rituximab+IVIG), compared to TAU, on secondary endpoints of 1.) supplemental oxygen requirments; 2.) six-minute walk distances (6MWD); 3.) adverse events, and; 4.) the number of AE-IPF relapses after initial responses to therapy.
Study Design:	Following baseline screening assessments, all patients at all sites that meet all inclusion/exclusion criteria (including confirmation of their eligibility by another study investigator) will be randomly assigned to receive one of the following treatments in a ratio of 2:1: • **Arm A** (n=34) **- Experimental Treatment**: Steroids: Prednisone 60 mg (p.o.) on day 1, followed by 20 mg/day on days 2-5, 7-14, and 16-19 (or the i.v. methylprednisolone equivalent). Methyl-prednisolone 100 mg i.v. will be administered on days 6 and 15, as a premedication prior to the rituximab. Insertion of a dialysis/apheresis catheter into a central vein, and initiation of

	therapeutic plasma exchange (TPE), rituximab, and intravenous immunoglobulin (IVIG) regimens: Therapeutic Plasma Exchange (TPE) will consist of 1x estimated plasma volume exchanges for 3 successive days (1-3) and then, after a one day interval to enable equilibration of autoantibodies between intra- and extra-vascular spaces, again on days 5, 6, 9, 11, 13, and 15. Rituximab: One gm i.v. will be administered on day 6 and day 15 after completion of the TPE on those days. Intravenous immunoglobulin (IVIG): 0.5 gm/kg/day i.v. on days 16-19 • **Arm B** (n=17) **– Treatment as Usual (TAU)**: The same steroid regimen as described for Arm A, i.e., prednisone 60 mg (p.o.) on day 1, followed by 20 mg/day on days 2-5, 7-14, and 16-19 (or the i.v. methylprednisolone equivalent), and methylprednisolone 100 mg i.v. administered on days 6 and 15. All patients enrolled in both cohorts at all sites will also receive empiric broad-spectrum antibiotics for 8 days. The empiric antibiotic regimen will be reassessed and tailored based on any subsequent cultures and sensitivity results. Patients will be monitored carefully for occurrences of adverse events, laboratory test abnormalities, and changes in vital signs. The respective treatment courses can be finished on an outpatient basis among enrolled patients who are able to be discharged from the hospital, if medically indicated, and if those treatment compliance can be assured. Patients will be followed for the duration of their hospital admission after enrollment, and then observed as either inpatients or outpatients on days 19, 60, 90, 180, 270, and 365. A telephone contact will occur at monthly intervals, aside from those visits above. The total observation/subject is 365 days.
Planned Sample Size:	A total of 51 subjects will be enrolled in this multi-center trial from the 6 participating medical centers (34 experimental and 17 TAU). It is anticipated that each site will enroll approximately equal numbers of subjects (e.g., ~9 each) over the duration of this project.
Duration of Treatment:	19 days
Inclusion Criteria:	1.) Age between 40-85 years old. 2.) A diagnosis of IPF that fulfills ATS/ERS Consensus Criteria.[1] 3.) Hospitalized patient with a diagnosis of AE-IPF, as ascertained by the responsible Primary Investigator (PI), with findings that include worsening or new development of dyspnea or hypoxemia within the last 30 days.

	4.) Ground-glass abnormality and/or consolidation superimposed on a reticular or honeycomb UIP pattern on locally read chest CT scan. 5.) Ability and willingness to give informed consent and adhere to study requirements.
Major Exclusion Criteria:	1.) Diagnoses of current infection per clinical or microbial assessments. 2.) Diagnoses of an additional or alternative etiology for respiratory dysfunction based upon clinical assessment, including congestive heart failure, sepsis, thromboembolism, etc, 3.) History or serological evidence of hepatitis B, or current hepatitis C infection. 4.) Coagulopathy, defined as an INR >1.6, PTT > 2x control, fibrinogen <100 mg/dL, or platelet count <50K unless these abnormalities can be reversed safely. 5.) Hyperosmolar state or diabetic ketoacidosis to suggest uncontrolled diabetes, or uncontrolled hypertension (systolic BP >160 mm Hg and diastolic BP >100 mm Hg) that would contraindicate use of corticosteroids. 6.) Hemodynamic instability, defined as an inotrope or vasopressor requirement. 7.) History of reaction to blood products or murine-derived products. 8.) Active malignancy or undergoing treatment of malignancy, excluding basal or squamous cell skin cancer and low-risk prostate cancer, the latter defined as stage T1 or T2a, with prostate specific antigen (PSA) less than 10 ng/dl. The experimental treatments are not known to promote cancer progression, and these criteria are within current guidelines. 9.) Unwillingness to accept blood product transfusion. 10.) Diagnosis of major comorbidities, or other considerations, that the responsible physician-investigators believe should disqualify subjects, or are expected to interfere with study participation. 11.) Treatment for >14 days within the preceding month with >20 mg. prednisone (or equivalent) or any treatment during the last month with a cellular immuno-suppressant (e.g., cyclophosphamide, methotrexate, calcineurin inhibitors, mycophenolate, azathioprine, etc.). An exception will be made if the patient has a bronchoalveolar lavage (BAL) negative for pathogens. 12.) Presence of a condition or ongoing treatment with a medication that precludes TPE. 13.) Concurrent participation in other experimental trials. 14.) Fertile females who do not agree to contraception or abstinence, or have a

	positive pregnancy test (urine or blood). IPF is a disease of older adults, and male predominant, so this will not be a frequent consideration. 15.) Presence of positive (abnormal) classical autoimmune tests: ANA, RF, Anti-SSA, and Anti-CCP. This criterion will eliminate patients with confounding classical autoimmune syndromes. Many IPF patients will have already had these tests, which are standard of practice (SOP) at many IPF centers, and these prior results will suffice if the tests were performed within the last year. Otherwise, these tests need to be performed prior to enrollment and they can usually be procured in 1-2 days. ANCA will continue to be tested during screening but negative results are no longer a requirement for randomization. Based on experience, we anticipate ~10% of patients who fulfill all other IPF criteria will nonetheless be positive for one of these classical autoantibody tests. 16.) IgA deficiency (IgA level <7 mg/dL)- to preclude IVIG reactions. 17.) Listed with the United Network for Organ Sharing for lung transplant <u>at the time of enrollment</u>. 18.) Patients who are intubated at time of STRIVE enrollment. 19.) Prior use of rituximab within the year preceding enrollment. 20.) Clinical or Morphologic Domain criteria of IPAF.[2]
Study Endpoints:	• <u>Primary endpoints</u>: The primary end-point is 6-month survival. Deaths from any cause are uncensored. Lung transplantations, if any, will be censored events. • <u>Secondary endpoints</u>**:** Secondary end-points are: a.) treatment-related effects on supplemental O2 requirements; b.) 6MWD; c.) adverse event (AE) rates; and d.) number of AE-IPF relapses

1. OBJECTIVE, SPECIFIC AIMS, BACKGROUND, AND SIGNIFICANCE

1.1 OBJECTIVE

The primary goal of this randomized, multi-center, open-label Phase IIb clinical trial is to determine effects of combined therapeutic plasma exchange (TPE), rituximab, and intravenous immunoglobulin (IVIG), in comparison to standard, conventional treatment as usual (TAU), on the survival of patients with acute exacerbations of idiopathic pulmonary fibrosis (AE-IPF).

1.2 SPECIFIC AIMS

<u>Hypothesis:</u>
Our central hypothesis is that ***AUTOANTIBODY REDUCTION IS BENEFICIAL FOR AE-IPF PATIENTS***. We propose to test our central hypothesis by examining selected effects of TPE *plus* rituximab *plus* IVIG on AE-IPF patients.

Specific Aims:

Specific Aim 1: To conduct a Phase IIB clinical trial in 51 hospitalized AE-IPF subjects at four major medical centers. Subjects will be randomized 2:1 into the experimental arm or control arm (treatment as usual [**TAU**]), respectively. The primary endpoint of this trial will be a comparison of six-month survival.

We hypothesize the experimental therapy will improve six-month survival of AE-IPF patients.

Specific Aim 2: To determine effects of the experimental regimen in AE-IPF patients, compared to TAU, on four secondary endpoints: **A.)** Changes in supplemental oxygen requirements pretreatment and after completion of therapy on day 19, as well as on days 60, 90, 180, 270, and 365; **B.)** Six-minute walk distances (6MWD), which are facile, inexpensive, integrative measures of cardiopulmonary function, measured at the same times. These longitudinal O_2 and 6MWD measures will enable us examine the duration of treatment effects; **C.)** Adverse event rates (e.g., comparative frequencies of infections, catheter-related problems, hemodynamic or metabolic perturbations, and other complications); and **D.)** The number of AE-IPF relapses following initial responses to therapy.

We hypothesize the experimental therapy will improve pulmonary gas exchange and functional capabilities of AE-IPF patients, and have an acceptable adverse event profile.

1.3 BACKGROUND:

Idiopathic pulmonary fibrosis (IPF) is a fibroproliferative lung disease of older individuals that causes unremitting dyspnea and hypoxemia.[1] The disease usually progresses relatively slowly, if episodically, and median survival is ~3 years. However, a sizeable proportion of idiopathic pulmonary fibrosis (IPF) patients, variously estimated as 10%-50**%,** develop acute exacerbations of their lung disease (AE-IPF) that are not attributable to other causes.[3] Because the etiology of AE-IPF is enigmatic, it has been impossible to rationally select agents that specifically target the underlying pathological mechanism(s). No medical intervention yet tried has efficacy for AE-IPF, and these patients have very poor prognoses.[1,3-7] Recent studies have revealed several parallels between conventional autoimmune syndromes and progressive IPF. On the basis of considerable data (to follow), we believe that antibody-mediated autoimmunity plays an important role in AE-IPF.

The role of immune processes in IPF has generally been discounted, primarily because this lung disorder does not respond to glucocorticoids. However, many other **antibody-mediated lung diseases** are similarly resistant to steroids and nonspecific agents. Among these examples, granulomatosis with polyangitis ("Wegener's syndrome"), Goodpasture's syndrome, acute interstitial lung diseases (ILD) associated with polymyositis, rheumatoid arthritis (RA), or other classical autoimmune diseases, and lung transplant rejection due to alloantibodies, also have very high rates of progression and mortality when treated primarily (or solely) with steroids.[8-19] In contrast, targeted treatments that reduce autoantibodies are frequently beneficial for these syndromes. The experimental AE-IPF therapy proposed in this clinical trial was adapted from regimens used in other antibody-mediated lung diseases.[8-15]

While considerable effort has been directed at understanding and treating IPF *per se*, and two therapeutic agents for the disease were recently approved, AE-IPF is comparatively understudied, despite the lethality of this syndrome. The results of this clinical trial could provide **compelling evidence** that autoantibody reduction therapy benefits AE-IPF patients. *This trial has the potential to be paradigm-shifting, alter current approaches to AE-IPF treatment, and could ultimately save the lives of untold future patients.*

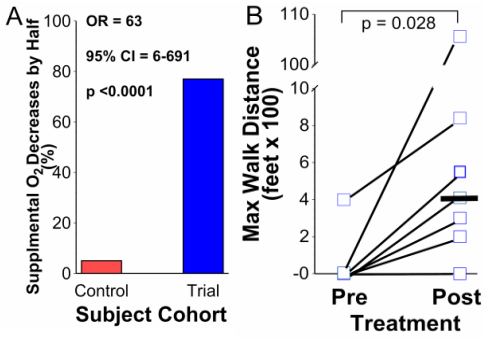
PRELIMINARY DATA:

Autoantibody Reduction Therapy in AE-IPF Patients: We conducted a pilot trial of autoantibody reduction in AE-IPF patients at the University of Pittsburgh Medical Center (UPMC) (n = 10) and University of Texas Medical Branch (n = 1).[27] All were admitted to ICUs or specialized high-level respiratory care units for **severe, rapidly worsening** AE-IPF.[3-7] None had other causes of lung dysfunction or conventional autoimmune diseases. None were eligible for transplantation due to age, irreparable coronary artery disease, or being too ill to have necessary evaluation procedures (e.g., heart catheterizations, colonoscopies, etc.).

We empirically developed and optimized a protocol now consisting of 9 TPE treatments over 15 days *plus* 2 doses of rituximab *plus* 4 days of intravenous immune globulin (IVIG).[27] TPE rapidly removes circulating autoantibodies and can result in dramatic clinical improvement,[17,18,29] as it did in all but two AE-IPF patients. Rituximab depletes autoantibody-producing B-cells, but it's onset of action may take weeks or months.[9,11-13] IVIG has many effects on autoantibody production, and is often added to TPE and/or rituximab to treat autoimmune diseases.[17,19,29] Subject outcomes were compared to a cohort of 20 AE-IPF patients admitted to UPMC prior to the pilot trial. The historical controls fulfilled the same criteria as trial subjects.[27]

We found the experimental therapy improved gas exchange, walk distances, and survival of AE-IPF patients in pilot trials (Figures 1 and 2).

Figure 1. (*right*) **A.**) Requirements for supplemental O_2 decreased in 11/13 treated subjects, and by more than 50% in 10 (compared to one reduction among 20 historical controls) (OR = Odds Ratio). **B.**) Maximal walk distance (not a formal 6MWD) was measured in the last 7 treated patients. All but one increased by ≥100%. Horizontal bar denotes median. Walk distances were not systematically recorded in historical controls, but only one patient clinically improved during their hospitalization.



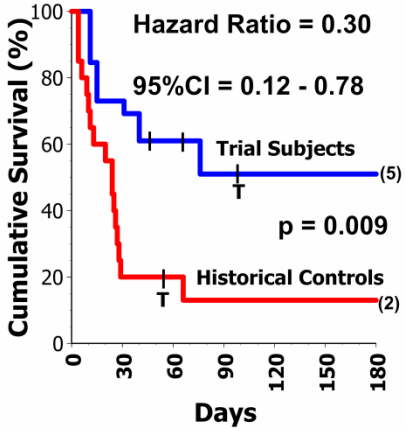


Figure 2. (*left*) A.) AE-IPF patients treated with autoantibody reduction therapy (n = 13) had better 6-month survival (51%) than the 20 historical controls (13%). Cross-hatches and numbers in parenthesis denote censored events (end of observations), including lung transplants, which are indicated by T.

Underlying Biology: Numerous, interrelated pathological B-cell abnormalities that are diagnostic for autoantibody syndromes are also present in IPF patients, especially among those with progressive disease:

B-cells in IPF Lungs: We have found highly abnormal focal B-cell infiltrates, particularly near fibroblast foci, in every IPF lung we have examined (Figure 3),[25,28] and others report similar results.[30-34] In diseases other than IPF, B-cell infiltrates in diseased tissues are recognized as an abnormal feature of an immunological disorder.[35,36] Moreover, the B-cells within these infiltrates

typically produce vasoactive, profibrotic, and proinflammatory mediators, as well as antibodies (or autoantibodies).[36] **A very recent study confirmed B-cells are especially prevalent in AE-IPF lungs**.[34]

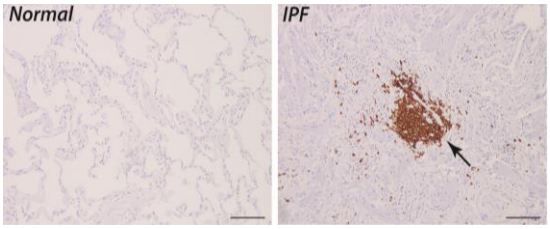


Figure 3. Intrapulmonary B-cells. Normal lung (*left panel*) and IPF lungs (*right panel*) immunostained for CD20 (specific for B-cells). These B-cells have immigrated from extrapulmonary origins, being only infrequently positive for Ki-67 (x100).[25,28]

Autoantibodies in IPF: Many different autoantibodies have been detected in IPF patients by use of various methods.[20,23,24,27,37-46] **The concurrent presence of diverse autoantibodies is a characteristic feature of autoimmune syndromes.**[47-50] We found IgG autoantibodies in >80% of a cross-sectional cohort of mostly stable IPF in an early assay,[20] and in >90% using new, more sensitive methods (manuscript in preparation).

All AE-IPF tested so far (n=16) had circulating IgG autoantibodies detected by HEp-2 indirect immunofluorescence assays (IFA) (Figure 3), [27] whereas ~10% of healthy controls have weak positive IFA.[47]

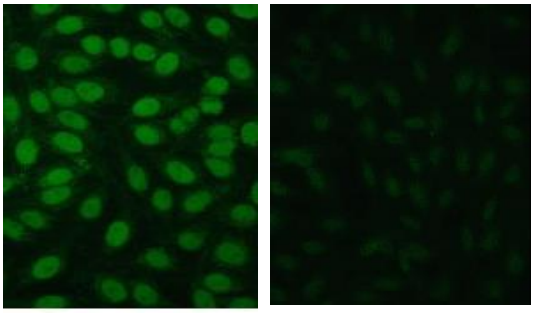


Figure 3. (*right*) HEp-2 IFA, which are universally positive in AE-IPF patients, simultaneously detect any/all anti-HEp-2 autoantibodies. *Left panel* is AE-IPF plasma (1:40 dilution) *right panel* is normal plasma. [24,27]

Do These IPF Autoantibodies Do Anything? IPF autoantibodies can have deleterious effects, and are not merely epiphenomenal:

A.) Cytotoxicity: IgG autoantibodies can aggregate antigens and form immune complexes (IC) in tissues. IC activate NK cells and complement, which are highly cytotoxic.[51,52] IC and complement also trigger cascades that have multiple downstream effects, including neutrophil recruitment.[51] These processes are very abnormal and are universally recognized as being highly pathogenic in other diseases.[51,53,54]

IC are also present in the circulation,[37,55] bronchoalveolar lavage (BAL),[56] and lung parenchyma of IPF patients,[24,25] especially among those with AE-IPF (Figure 4). Complement deposits are also prevalent in IPF lungs,[24,25] again, particularly in AE-IPF (Fig. 4). **It is very unlikely these abnormalities are benign**.[36,51-54]

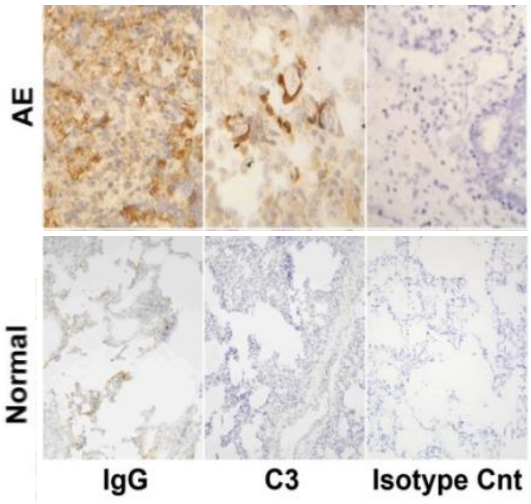


Figure 4. (*left*) Replicate studies show immune complex (IgG) and complement (C3 or C4d) deposits are common in IPF lungs.[24,25] These abnormalities are even more striking in AE-IPF lungs explanted during emergent transplantations ("AE" – top row). Normal lungs are shown in the bottom row, and isotype controls (Cnt) are shown in far right columns.

B.) Physiological Actions: Autoantibodies can also **alter cell functions** by various mechanisms which include binding to surface receptors that transduce signals.[20,52,54,57,58,60]

We discovered IgG autoantibodies against heat shock protein 70 (HSP70) in 25% of a cross-sectional IPF cohort, 50% of those who died, and 70% of the AE-IPF patients (p<0.001).[23,24] Anti-HSP70 IgG portends a poor prognses in IPF (Figure 5).

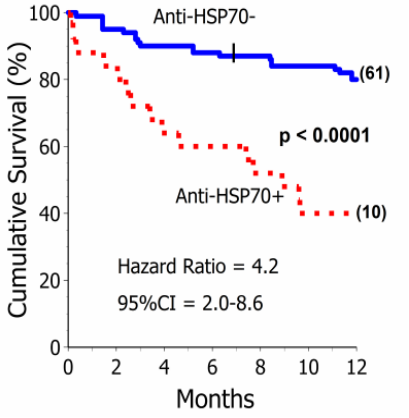


Figure 5. *(right)* IPF patients with HSP70 autoreactivity have worse survival.[23]

In addition to function as an intracellular protein chaperone, HSP70 is exported extracellularly by stressed cells.[57-60] Extracellular HSP70 acts like a cytokine, binding to and stimulating various cell surface receptors, including scavenging receptors and CD33-related lectins.[57,58]

We isolated anti-HSP70 IgG from several AE-IPF plasmas by protein G and affinity columns. These cross-link and stimulate HSP70-receptor complexes on target cells and, among other effects, increase apoptosis resistence and production of IL-8 (Figure 6).

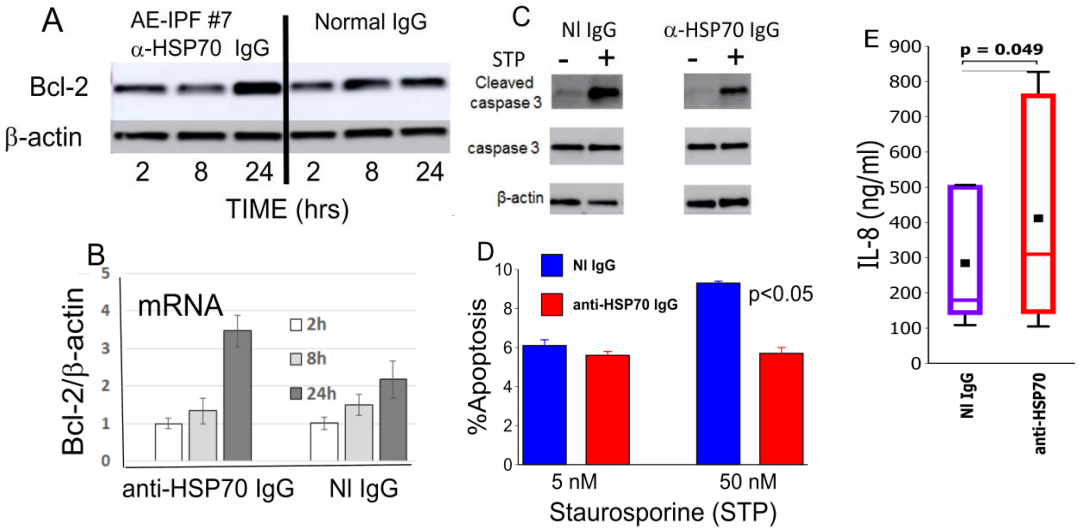


Figure 6. (**A** and **B**) Sub-physiological concentrations (1 μg/ml) of anti-HSP70 IgG autoantibodies, isolated from AE-IPF patients, bind to HSP70 on surfaces of primary human lung fibroblast surfaces (not shown), and increase fibroblast Bcl-2 protein and mRNA productions. The treated fibroblasts become resistent to apoptosis induced by staurosporine (STP), as ascertained by caspace 3 (**C**) and vital dye exclusion (**D**). Apoptosis resistence of fibroblasts has been implicated in IPF pathogenesis.[61] Data represent replicate experiments in 3 primary normal fibroblast lines each treated with 3 different AE-IPF patient anti-HSP70 IgG. **E**.) We previously showed IPF anti-HSP70 increased monocyte production of IL-8, [23] another mediator of IPF. These autoantibody effects on fibroblasts and monocyte lineage cells are mediated by AKT and JNK pathways (not shown), and are consistent with known biological actions of receptor-bound HSP70[58-60] (manuscript in preparation). NI IgG = normal IgG.

Numerous other IPF autoantibodies also have deleterious effects on various target cells, such as direct cytopathy, and/or increasing productions of inflammatory or fibrotic mediators.[38,40-42,44-46]

More Features of Autoimmunity in IPF: Space constraints preclude detailed presentations of all the parallels between conventional autoantibody syndromes and progressive IPF. In brief these include:

B-cell Mediators in IPF: **B-lymphocyte Stimulating Factor** (BLyS, *aka* BAFF) is a trophic factor for B-cell survival, maturation, and autoantibody production.[61] Plasma BLyS levels are increased in autoantibody disorders (e.g., SLE, RA, etc.),[62-64] and this mediator is also pro-fibrotic.[65] We found BLyS levels are abnormally increased in IPF patients and inversely correlated with lung function and outcomes.[25] **C-X-C motif chemokine 13 (CXCL13)** mediates B-cell homing to inflammatory foci and is important in the genesis of autoimmunity.[66-70] We found CXCL13 is over-expressed in AE-IPF and inversely correlated with survival,[28] and these findings have been corroborated.[33]

T-cells and HLA: Production of IgG autoantibodies with specificities for peptides requires help from T-cells that share avidity for those autoantigens.[71] T-cell autoimmunity is near ubiquitous in autoimmune diseases, **and we find it is also present in IPF**.[20,23] Other studies show T-cell differentiations in IPF patients that typify immune disorders, and are predictive of poor outcomes.[21,26,72] HLA allele biases are another hallmark of autoimmunity.[73] We found HLA-biases **in IPF patients**[22] and these associate with specific autoantibodies.[23]

How Does Autoimmunity Arise? Autoimmunity often develops subsequent to other injurious processes such as infections, cancer, etc., [**and, perhaps, the primary injury of IPF?**] by epitope spread or mimicry.[74-79] "Secondary" autoimmunities may be benign, but in many cases these "new" immune responses cause striking additional morbidity, e.g., carditis or nephritis following otherwise self-limited *Streptococcal* infections, neurologic syndromes associated with cancer, etc.[74-77]

1.4 SIGNIFICANCE

If our central hypothesis is correct, the experimental therapy here, mechanistically targeted to reduce autoantibodies, could result in significant benefit for a lung disease syndrome that has, until now, been almost invariably inexorable. *This clinical trial has the potential to profoundly affect current paradigms and treatment approaches to AE-IPF, and could ultimately be broadly relevant to IPF patients with more slowly progressive disease*

2 RESEARCH DESIGN AND METHODS

2.1 CLASSIFICATION AND METHODOLOGICAL DESIGN

This is a randomized, multi-center, open-label Phase IIb clinical trial to determine the efficacy of combined therapeutic plasma exchange (TPE), rituximab, and intravenous immunoglobulin (IVIG), in comparison to treatment as usual (TAU), among patients with acute IPF exacerbations.

2.2 STUDY DESIGN

Subjects will be recruited from the inpatient populations of the collaborating institutions. The primary care physician/clinical care team, who may be study investigators or colleagues of the study investigators, will first identify potential research subjects and obtain their approval for discussion of the research project with the study investigators.

Following procurement of informed consent and completion of baseline/screening assessments, study subjects (total n=51) will be randomized 2:1 into one of two treatment arms: the combined TPE, rituximab, and IVIG (experimental therapy) vs. TAU. It is anticipated that each site will enroll approximately equal numbers of subjects (e.g., ~13 each) over the duration of this project.

Subject eligibility will be confirmed prior to randomization by an adjudication process. After screening, but immediately prior to randomization, the PI who is evaluating the potential subject will notify PIs at the other centers by cellphone and email messaging, to inform them a patient seems eligible. The initiating PI will then send out a checklist of the randomization criteria, along with a provision for free-text comments, as they apply to the individual subject, by text mail and email (the redundancy will preclude missed enrollments if one or more cellphone batteries are discharged, or a PI(s) is off-line). The randomization will proceed after confirmation of the diagnoses, and edibility is attested by at least one PI (or one of more Co-investigator if all the other PIs are unavailable). In the event of disagreement, the randomization will not progress until a clear majority of PIs concur, either for or against randomization. In these challenged cases, which are expected to be rare, the consensus (either for or against randomization) can be obtained by telephone conversation, cellular texts, or emails, after careful review of pertinent data, that could including radiology reports or deidentified images or other necessary information. Clinical co-Investigators will "vote" only if there is no other participating PI available, or in cases of otherwise unresolvable ties among the PIs.

All patients enrolled in both cohorts will receive a standardized steroid dosing regimen (for 19 days), as well as empiric antibiotics for 8 days (to follow), as per clinical standards. The empiric broad-spectrum antibiotics will be initiated soon after admission, and the will be reassessed and tailored based on the subsequent cultures and sensitivity results. Subsequent treatments with steroids and antibiotics will be at the discretion of the attending physicians, based on their clinical assessments.

Patients will be monitored carefully for occurrence of adverse events, laboratory test abnormalities, and changes in vital signs. Adverse events will be evaluated according to criteria outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

The treatment protocol will last for 19 days. Enrolled patients may be discharged from the hospital prior to the completion of the 19 day therapy, if medically indicated per their attending

physicians, and if they can still receive their study treatments and maintain protocol compliance as outpatients. Conversely, enrolled subjects still hospitalized on day 20 will be followed for the duration of their hospital stay. Patients removed from the study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Subjects discharged from the hospital will be encouraged to return as outpatients for observations and specimen acquisitions on days 60, 90, 180, 270, and 365. Telephone interview to detect potential late complications and outcomes will be conducted by study coordinators at other monthly intervals.

2.3 STUDY TREATMENTS

Following confirmation that patients meet all inclusion/exclusion criteria (Section 3.2) and have completed the informed consent process and baseline screening assessments, participants will be randomly assigned to receive one of the two following treatments, starting on Day 1, in a ratio of 2:1.

1.) EXPERIMENTAL TREATMENT (n=34): Subjects will be treated with 60 mg prednisone p.o. on day 1, followed by 20 mg prednisone/day p.o. thru day 19, except on days 6 and 15. Methylprednisolone (Solumedrol) i.v. at equivalent doses may be used in lieu of prednisone. On days 6 and 15 subjects will receive 100 mg Solumedrol i.v., as a premedication for rituximab. Steroid dosing after day 19 will be at the discretion of the attending physician. There is no evidence that any steroid regimen has efficacy for AE-IPF.[1-4] Nonetheless, these agents are **standard of practice** (**SOP**) for AE-IPF patients with widely varying dosing regimens.[1]

In addition: The experimental trial subjects will also have a dialysis/pheresis catheter placed in a central vein, followed by therapeutic plasma exchanges (TPE), rituximab, and IVIG.

-TPE consist of 1x estimated plasma volume exchanges for 3 successive days (days 1,2, and 3), followed by two more daily treatments on days 5 and 6, and then four more q.o.d. (days 9,11,13, and 15). Initial daily TPE is intended to promptly decrease autoantibody titers in these rapidly progressive subjects. Subsequent interrupted scheduling will allow equilibration of tissue-bound autoantibodies into the circulation, thereby increasing TPE efficacy. The 48 hour interruption (days 7-8) is to enable the first dose of slow-onset rituximab to be administered early, rather than later (after all TPE). Spacing of 48 hrs between rituximab and the next TPE prevents removal of the anti-B-cell agent (Dr. Paul Brunetta, Genentech, pers. comm.).

Plasma fluid volume will be replaced during TPE with 5% albumin, to maintain a net fluid balance of 95-100%. In the event a subject's fibrinogen is <120 mg/dL at the initiation of a TPE, as may occur in later treatments, either (1) cryoprecipitated antihaemophilic factor (AHF) (two 5-pooled units) will be given prior to the procedure to raise the fibrinogen level or (2) the replacement fluid will be 50% plasma and 50% 5% albumin, in order to maintain post-procedural fibrinogen >50 mg/dL and thus, minimize bleeding risks. The use of cryoprecipitated AHF prior to the procedure or plasma as the replacement fluid during the procedure will be at the discretion of the attending apheresis physician. Calcium supplementation, either by po or by IV, may be given to reduce citrate toxicity related to TPE. Dialysis catheters are removed after the last TPE, when the fibrinogen level is >100 mg/dL.

-Rituximab: One gm i.v. will be administered on day 6 (after completion of that day's TPE) and again on day 15, after the last TPE. This regimen was adopted from the protocol of an ongoing IPF trial (ART-IPF) and has been well tolerated. Subjects will be premedicated with acetaminophen, diphenhydramine, and methylprednisolone 100 mg i.v., to obviate reactions.

-IVIG: Doses of 0.5 gm/kg will be administered on days 16-19, after the last TPE. Subjects who have mild reactions will be premedicated, as for rituximab, prior to subsequent doses. This is also SOP for lung transplant recipients treated with IVIG for antibody-mediated allograft rejection in our hospitals.

-Empiric Antibiotics: All subjects, at all sites, in both treatment arms, will receive antibiotics for 8 days, **a SOP** for empiric therapy of patients with exacerbations of chronic lung diseases, based on recognition that bronchoalveolar lavage (BAL) and transtracheal aspiration (TTA) have poor diagnostic accuracy. Empiric antibiotic therapy for AE-IPF is widely accepted. The 8 day duration is based on data in other seriously ill patients. Our SOP regimen is: azithromycin (until *Legionella* DFA is negative) plus piperacillin/tazobactam + vancomycin. Substitutions for allergies are ciprofloxacin and linezolid, respectively. Antibiotics will be administered as specified by package inserts. Subjects intubated after enrollment will be managed using standard ARDS Network guidelines.

The duration of this antibiotic regimen can be shortened, at the discretion of the attending physician, among patients who have been treated with an identical (or clinically comparable) regimen, at the time of or immediately prior to enrollment in STRIVE-IPF (e.g., patients who were getting antibiotics at an outside hospital prior to transfer to the study site). Given difficulties in diagnosing infections in these often critically ill patients (see Infectious Considerations Section 3.3), the AE-IPF subjects in this trial should receive appropriate antibiotics, but consideration for adjustment is necessary in cases in which the total duration of antibiotic therapy would be excessive and potentially deleterious.

2.) TREATMENT AS USUAL (TAU) Controls (n=17): The subjects in this arm will receive the same steroid regimen at the Experimental Arm Subjects: 60 mg prednisone p.o. on day 1, followed by 20 mg prednisone/day p.o. thru day 19, except on days 6 and 15. Methylprednisolone i.v. at equivalent doses may be used in lieu of prednisone. On days 6 and 15 subjects will receive 100 mg Solumedrol i.v. Steroid dosing after day 19 will be at the discretion of the attending physician.

All TAU subjects will also receive the identical empiric antibiotic regimen as the Experimental Treatment Arm subjects (see details above).

2.4 RANDOMIZATION

A randomization list, (2:1 experimental arm to controls) will be generated in advance by the Data Coordinating Center (DCC) and programmed into the web-based data entry and management system. Subjects will be stratified by disease severity as either **A.) Mild** (In order maintain $S_aO_2 \geq 93\%$, supplemental O_2 requirement are less than or equal to either 5L/min by nasal cannula or 50% O_2 by face mask) or **B.) Severe** (Supplemental O_2 requirements > either 5L/min or >50% O_2 per face mask). Subjects will also be stratified based on their use or nonuse of any/both antifibrotic medications (nintenanab and/ pirfenidone), with 2 to 1 randomization within strata. Due to the small sample size, stratification by site will not be attempted.

2.5 STUDY TREATMENT SCHEMATIC

The experimental interventions (days 1-19) are outlined below in Table 1:

Days on Intervention	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Prednisone or equivalent (p.o. dose per day)	**60 mg**	**20 mg each day**				**none**	**20 mg each day**								**none**	**20 mg each day**			
Therapeutic Plasma Exchange (TPE)	**TPE, each of these days**				**TPE, each of these days**				**TPE**		**TPE**		**TPE**		**TPE**				
Rituximab						**1 gm IV**									**1gm IV**				
Acetaminophen (prior to Rituximab)						**650 mg Oral**									**650 mg Oral**				
Solumedrol (prior to Rituximab)						**100 mg IV**									**100 mg IV**				
Benadryl - diphenhydramine (prior to Rituximab)						**50 mg Oral**									**50 mg Oral**				
Antibiotics	x	x	x	x	x	x	x	x											
IVIG																**0.5 gm/kg/day**			
Experimental Blood Specimens	**Before therapy**																		
O_2 requirement assessment	**Before therapy**																		**After therapy**
TPE Collection	**500 ml + 50 ml**		**50 ml**						**50 ml**						**50 ml**				
6 minute walk distance	**Before therapy**																		**After therapy**

Table 1. Outline of Experimental Arm Procedures. Notes: Maintenance steroid doses after Day 19 are at discretion of attending physician(s). Later surveillance, endpoint measures, (and specimen acquisitions) are not shown here (days 60, 90, 180, 270, 365), or telephone contacts (end of months 1, 4, 5, 7, 8, 10, 11). Adverse events are prospectively recorded at these time points too, and at any time they may arise.

2.6 RELAPSES AMONG SUBJECTS

The duration of a single treatment course will almost certainly be finite, although several subjects have had prolonged remissions after the experimental therapy (Fig. 2, see also[27]). Patients with other autoantibody diseases who respond to analogous therapy often get consolidation therapy to sustain their remissions. We do not believe consolidation therapy can be incorporated into this trial. The **first principle here is to assess benefits of autoantibody-targeted therapy**. If so, later trials can focus on prolonging remission durations with consolidation therapies (if necessary). Nonetheless, patients who respond to their therapies in

either treatment arm may be given the benefit of comparable therapies if their AE-IPF flares again.

Two patients to date responded well to the experimental regimen and were discharged from the hospital with much lower O_2 requirements and ambulatory abilities, but again developed recurrent symptoms of increasing dyspnea and hypoxemia about 3 months later. Both responded to an abbreviated treatment protocol, adopted from analogous regimens used to treat other relapsing autoimmune disorders, consisting of five TPE administered every other day followed by four successive doses of IVIG (0.5 g/kg/day). Both subjects again responded, and were discharged and have had prolonged remissions. Another subject experienced a relapse within a few days of a successful initial treatment, while he was awaiting hospital discharge, and he too responded to the abbreviated treatment protocol.

Hence, subjects in either arm that had a favorable clinical response lasting for at least 5 days after completion of their initial treatment, will be eligible for retreatment one time during their 6 month participation in this trial.

For purposes here, a relapse is defined as a recrudescence of AE-IPF symptoms and physical findings, i.e., new or increased shortness of breath or hypoxemia during the last 30 days, without other explicable etiology. The presence of a relapse will be confirmed by adjudication among the PIs, following the same communication and survey procedures used to adjudicate and confirm the initial diagnoses of AE-IPF (see page 14).

The definition of a "favorable clinical response" is based on our clinical secondary endpoints, and consists of either a reduction in requirement for supplemental oxygen by 50% or an improvement of 6MWD by 30 m (see page 24).

The treatment of an AE-IPF relapse in a participant is based on their initial randomization.

All subjects will again be treated with 60 mg prednisone p.o. (or methylprednisolone equivalent) on day 1, followed by 20 mg/day for the duration of their therapy, and the specified empiric antibiotic regimen. In addition:

A.) Experimental arm subjects who relapse will receive TPE x 5, administered every other day, followed by four successive doses of IVIG (0.5 g/kg/day). A 50 ml aliquot from the first TPE discard will be collected, stored, and used in experimental assays.

B.) TAU subjects will again be treated with the steroids and antibiotics.

Second relapses, if they occur within the 6-month trial participation, will be treated with standard therapy (i.e., TAU).

All subjects with relapses will have 20 ml blood obtained for experimental purposes prior to beginning their respective "salvage" therapies. Assays (e.g., HEp-2 titers, IgG levels, particular autoantibody levels, or other immune mediators) in these specimens could be especially valuable to identify immune parameters that are associated with, and possible predict, AE-IPF recurrences.

2.7 STUDY PROCEDURES

Routine clinical care for seriously ill patients with respiratory insufficiency will be followed as ordered by the primary physician. The study will log the results of specific screening-baseline measures, coagulation assays (which are mandated by this protocol in conjunction with TPE). The results of other selected tests that may be obtained during the routine provision of clinical care will also be logged. These may include: complete blood count (CBC), electrolytes, glucose, BUN, serum creatinine, ionized calcium, magnesium, phosphorus, albumin, liver function tests consisting of total bilirubin, aspartate alanine transaminase (ALT), and aspartate glutamine transaminase (AST).

The first batch of removed plasma from the day 1 TPE (as well as every third TPE thereafter (33,6,9)) will be aliquoted and stored frozen (-20^{o} or below) for later experimental studies.

An extra 39 ml of blood needed for experimental immunologic research studies will be obtained pretreatment. These and all other blood draws will utilize phlebotomy tubes with K_2-EDTA anticoagulant Subsequently, 29 ml of blood for testing will be procured on days 60, 90, 180, 270, and 365 after the start of therapy.

Enrolled subjects will be visited by study personnel on each day of their hospitalization.

The following information will be collected and entered into the study case report forms (CRFs) and/or web-based data collection system. All clinical and laboratory data are initially obtained for routine clinical care, and will be collected from medical records.

1. Physician names and contact information, general medical and surgical histories, co-morbidities, concurrent medications, and allergies.
2. Recording of vital signs, demographics, and medication regimen.
3. Review of medications
4. Brief assessment of symptoms.
5. Recording of laboratory and clinical testing results.

The schedule for patient assessment and data collection is outlined as follows.

2.7.1 Screening

Screening (one or more days prior to randomization): Patients will undergo screening assessments to determine that all inclusion/exclusion criteria are met prior to receiving the study drug treatments. The screening assessment may take place over more than one day. Eligible patients will adjudicated by review and if concurred to be eligible will have the study explained in detail and asked to provide Informed Consent.

The following tests and procedures will be performed after providing informed consent, but prior to randomization:

- Detailed medical history and demographics.
- Physical exam and inpatient progress assessment to include vital signs and blood pressure.
- Laboratory evaluations specific for Inclusion/Exclusion Criteria to include: hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb) and hepatitis C virus antibody (HCV Ab). tests, IgA, ANA, RF, anti-SSA, anti-CCP, pregnancy test, either urine or blood (if applicable). ANCA will also be performed at this time, but are not used to determine eligibility. If HCV Ab are positive, HCV nucleic acid PCR will be performed. A positive result with the HCV PCR is an exclusion criterion, whereas negative results of this test do not

preclude randomization.

2.7.2 Experimental procedures

Day 1 (Initiation of therapy):

Randomization should occur as soon as possible after meeting confirmed eligibility, but within a maximum of 48 hours after meeting all inclusion/exclusion criteria. Confirmation of eligibility by other study clinicians, as detailed in Section 2.2 Study Design (page 14) will be necessary prior to randomization. Patients that meet all inclusion/exclusion criteria (and confirmation as above) will be randomized to receive one of the study treatments described above in Section 2.3. In addition, the following data will be obtained (if not already obtained during screening):

- Physical exam and inpatient progress assessment to include vital signs and blood pressure.
- Laboratory evaluations (routine clinical care) that may include: complete blood count (CBC), electrolytes, glucose, BUN, serum creatinine, ionized calcium, magnesium, phosphorus, INR, albumin, liver function tests including of total bilirubin, aspartate alanine transaminase (ALT)
- Experimental immunologic assays with blood samples to be processed and stored frozen, for later batch shipment (while frozen) to the Clinical Coordinating Center (CCC)
- Initiation of common steroid therapy, if not already started (see Section 2.3)
- Initiation of common antibiotic regimen, if not already started (see Section 2.3)
- Record O2 requirement
- Six minute walk distance (6MWD). 6MWD = 0 among subjects unable to ambulate.
- Adverse Event (AE) assessment.

For subjects randomized to TPE:

- Laboratory evaluations: complete blood count (CBC), INR, electrolytes, ionized calcium level (at the discretion of the attending physician), fibrinogen level
- Dialysis catheter placement in a central vein among subjects randomized to experimental therapy
- First TPE (with collection of a discarded 500 ml and 50 ml plasma aliquots from this procedure)
- AE assessment

Day 2 (for subjects randomized to TPE):

- Laboratory evaluations: complete blood count (CBC), INR, electrolytes, ionized calcium level (at the discretion of the attending physician), fibrinogen level
- Second TPE
- AE assessment

Day 3 (for subjects randomized to TPE):

- Laboratory evaluations: complete blood count (CBC), INR, electrolytes, ionized calcium level (at the discretion of the attending physician), fibrinogen level
- Third TPE (with collection of a 50 ml discarded plasma aliquot from this procedure)
- AE assessment

Day 5 (for subjects randomized to TPE):

- Laboratory evaluations: complete blood count (CBC), INR, electrolytes, ionized calcium level (at the discretion of the attending physician), fibrinogen level
- Fourth TPE

- AE assessment

Day 6 (for subjects randomized to TPE):

- Laboratory evaluations: complete blood count (CBC), INR, electrolytes, ionized calcium level (at the discretion of the attending physician), fibrinogen level
- Fifth TPE
- Following completion of TPE: premedications and rituximab
- AE assessment

Day 9 (for subjects randomized to TPE):

- Laboratory evaluations: complete blood count (CBC), INR, electrolytes, ionized calcium level (at the discretion of the attending physician), fibrinogen level
- Sixth TPE (with collection of a discarded 50 ml plasma aliquot from this procedure)
- AE assessment

Day 11 (for subjects randomized to TPE):

- Laboratory evaluations: complete blood count (CBC), INR, electrolytes, ionized calcium level (at the discretion of the attending physician), fibrinogen level
- Seventh TPE
- AE assessment

Day 13 (for subjects randomized to TPE):

- Laboratory evaluations: complete blood count (CBC), INR, electrolytes, ionized calcium level (at the discretion of the attending physician), fibrinogen level
- Eighth TPE
- AE assessment

Day 15 (for subjects randomized to TPE):

- Laboratory evaluations: complete blood count (CBC), INR, electrolytes, ionized calcium level (at the discretion of the attending physician), fibrinogen level
- Ninth and final TPE (with collection of a discarded 50 ml plasma aliquot from this procedure)
- Following completion of TPE: premedications and rituximab
- AE assessment

Days 16-19 (for subjects randomized to TPE):

- IVIG each day at 0.5 gm/kg
- AE assessment

Day 19 (All Subjects):

- Record O2 requirement
- Six minute walk distance (6MWD). 6MWD = 0 among subjects unable to ambulate.

2.7.3 Follow-up monitoring

A variance of 5 days will be allowed for the telephone contacts to account for weekends or holidays. A variance of 10 days will be allowed for each outpatient follow-up visit for similar reasons, as well as potential logistic/transportation problems. If subjects remain hospitalized at these later dates, an identical evaluation and procedures will be performed (as feasible):

Day 30 (1st month):

- Telephone call (if discharged from the hospital, or personal visit if an inpatient) to access status (brief assessment of symptoms, and a review of medical or surgical histories).
- AE assessment

Day 60 (2nd month):
- Outpatient or inpatient evaluation, if admitted to the hospital for other reasons, to include directed physical exam, assessment of symptoms, and a review of interval medical or surgical histories
- Experimental immunologic assays (blood samples to be processed and stored frozen), for later batch shipment (while frozen) to the Coordinating Center
- O_2 requirement
- 6MWD
- AE assessment

Day 90 (3rd month):
- Outpatient or inpatient evaluation, if admitted to the hospital for other reasons, to include directed physical exam, assessment of symptoms, and a review of interval medical or surgical histories
- Experimental immunologic assays (blood samples to be processed and stored frozen), for later batch shipment (while frozen) to the Coordinating Center
- O_2 requirement
- 6MWD
- AE assessment

Day 120 (4th month):
- Telephone call (if discharged from the hospital, or personal visit if an inpatient) to access status (brief assessment of symptoms, and a review of medical or surgical histories).
- AE assessment

Day 150 (5th month):
- Telephone call (if discharged from the hospital, or personal visit if an inpatient) to access status (brief assessment of symptoms, and a review of medical or surgical histories).
- AE assessment

Day 180 (6th month):
- Outpatient or inpatient evaluation, if admitted to the hospital for other reasons, to include directed physical exam, assessment of symptoms, and a review of interval medical or surgical histories
- Experimental immunologic assays (blood samples to be processed and stored frozen), for later batch shipment (while frozen) to the Coordinating Center
- O_2 requirement
- 6MWD
- AE assessment

Day 210 (7th month):
- Telephone call (if discharged from the hospital, or personal visit if an inpatient) to access status (brief assessment of symptoms, and a review of medical or surgical histories).
- AE assessment

Day 240 (8th month):
- Telephone call (if discharged from the hospital, or personal visit if an inpatient) to access status (brief assessment of symptoms, and a review of medical or surgical histories).
- AE assessment

Day 270 (9th month):
- Outpatient or inpatient evaluation, if admitted to the hospital for other reasons, to include directed physical exam, assessment of symptoms, and a review of interval medical or surgical histories
- Experimental immunologic assays (blood samples to be processed and stored frozen), for later batch shipment (while frozen) to the Coordinating Center
- O_2 requirement
- 6MWD
- AE assessment

Day 300 (10th month):
- Telephone call (if discharged from the hospital, or personal visit if an inpatient) to access status (brief assessment of symptoms, and a review of medical or surgical histories).
- AE assessment

Day 330 (11th month):
- Telephone call (if discharged from the hospital, or personal visit if an inpatient) to access status (brief assessment of symptoms, and a review of medical or surgical histories).
- AE assessment

Day 365 (12th month)- final assessment:
- Outpatient or inpatient evaluation, if admitted to the hospital for other reasons, to include directed physical exam, assessment of symptoms, and a review of interval medical or surgical histories
- Experimental immunologic assays (blood samples to be processed and stored frozen), for later batch shipment (while frozen) to the Coordinating Center
- O_2 requirement
- 6MWD
- AE assessment

Every effort will be made to ascertain status among those seemingly lost to follow up by contacting patient or next of kin, conducting internet searches for obituaries, etc.

2.7.4 Specimen Collection and Management

Specimen Collection / Documentation: An extra 29 ml of blood for experimental immunologic research studies will be obtained pretreatment, and on days 60, 90, 180, 270, and 365 after the start of therapy. The peripheral blood will be processed to separate mononuclear cells, plasma, and sera, which will be aliquoted, and frozen (at -20° or below) until used in batched assays. The apheresis waste bag (plasma removed from the patient) during the first TPE and the last TPE will also be aliquoted and stored frozen, for additional assays. These assays will be carried out in the laboratories of Dr. Steven Duncan at the Clinical Coordinating Center (UAB) after batched overnight shipment of the specimens.

Each research sample will be labeled with subject's unique identifier, sample date, and sample collection time. The code number and date on which the specimen is frozen, all other information about the specimen, and subsequent processing will be entered on a specimen processing worksheet.

Covariate information, e.g., concomitant medications, laboratory values, etc., will be obtained at each time point.

Specimen Handling and Labeling (De-Identification)
All research specimens and all records associated with the samples will be labeled only with a unique code that links to the trial data, but contains no personal identifiers. The information linking these code numbers to the corresponding subject's identity will be kept in a secure location in the PI's office at each participating center, and will not be available to staff managing samples at the research laboratories.

Specimen Management and Storage: Specimens in excess of immediate assay requirements may be stored indefinitely in a secured freezer under the control of the responsible PI. The coding information linking patient identifiers to the stored samples will be maintained in a locked, secure area that will be accessible only to the study investigator. Subjects may request to have their samples destroyed at any time. These samples will be destroyed immediately upon receipt of the subjects' written request to do so.

Restrictions to Direct Access of Specimens: Specimens will be kept in the responsible study investigators' laboratories indefinitely and will be under the control of the PI. Investigators or other personnel not involved with the management or operations of the study are not permitted direct access to the specimens.

2.8 STUDY ENDPOINTS

2.8.1. The Primary End-Point
The primary endpoint of this trial is six-month survival. Patient survival is unequivocally important, objective, and accurately ascertained from observations, patient or family phone interviews, and internet obituary searches. The uncensored event will be death from any cause, with lung transplantations tabulated as censored events. Lung transplantations, or institution of extracorporeal membrane oxygenation (ECMO) will be used as events in sensitivity analyses to ensure the consistency of the outcome results, since these are likely informative censorings.

2.8.2. Secondary End-Points
General: O_2 requirements and six minute walks will be assessed immediately prior to treatment and after completion of therapy on day 19, as well as on days 60, 90, 180, 270, and 365. Subjects discharged from the hospital after completion of the protocol will be instructed to return to our clinics for these scheduled assessments. These visits and endpoint measures are already SOP in many IPF clinics. Adverse events and relapses that occur anytime during the subjects participation in this study will be recorded and compared.

A.) Supplemental O_2 requirements: are a reflection of lung function, and clinically important. O_2 measures, at the times specified above, will be tabulated as the flow rate (or concentration) necessary to maintain resting arterial oxygen saturations (per oximeter) at $\geq$93% (this gives some safety margin), as we used in the pilot trial.[27] Many air-hungry AE-IPF cannot tolerate a tight-fitting face mask, nor breathe thru a mouthpiece. Thus, we cannot systematically measure

F_IO_2, which precludes analyses of P_aO_2:F_IO_2.[27] Supplemental O_2 requirements over the various intervals will be dichotomously categorized into one of two groups for comparison: **1.) Improved** (reduced by ≥50%) or **2.) Unimproved** (reduced <50%, unchanged or worsened).

B.) Six minute walk distance (6MWD): will also be performed at those times described above. 6MWD are simple, inexpensive, reproducible, and SOP in IPF patients. 6MWD will be performed per ATS/ ERS guidelines, by trained nursing staff in hospital or clinic hallways (our SOP). Values for 6MWD can be obtained in all patients, even those who are bedbound (value = 0)(Fig. 1B). Only one AE-IPF so far could tolerate spirometry at enrollment, precluding systematic analyses of PFTs. 6MWD results over the various intervals will also be dichotomized into either **1.) Improved** (by ≥30 meters) or **2.) Unimproved** (improved <30 m., same, or worsened). The cutoff value of 30 m. ~corresponds to 6MWD minimal clinically important differences.

C.) Adverse events: The NCI Common Toxicity Criteria Scale will be used to define grades (severity) of adverse events and toxicities. An adverse event is defined as any untoward medical occurrence in a subject, regardless of its relationship to these treatments. Toxicity is an adverse event with a direct relationship to the study drug. All toxicities are adverse events, but not all adverse events are toxicities. Computer data entry (and case report forms- [CRF]) will require responses to all adverse events, with a particular focus on infections (including location and organism), catheter-related problems (e.g., bleeding, clot), apheresis-related complications (e.g., hypotension, citrate toxicity, etc), metabolic or hemodynamic perturbations (e.g., hyperglycemia, hypotension, etc.) and other, less frequent complications (e.g., neurologic symptoms), as well as having provision for free text entries. Recording all AEs in pre-specified checklists (and free text entries), will guard against unintended bias in this unblinded trial.

D.) AE-IPF Relapses. The number of relapses that occur in subjects in either study arm will be compared adjusted for duration of exposure (i.e. deaths have potentially less time in which to have a relapse and thus this will be used in the analyses). The definition of an AE-IPF relapse and the adjudication process used to confirm these diagnoses has been detailed on page 18.

2.8.3 Additional Studies That are Not Formal Endpoints

All these assays will be performed in the laboratory of Dr. Duncan, using stored (frozen) plasma specimens, batch-shipped from all sites:

A.) Anti-HEp-2 IFA Titers: Pretreatment autoantibody titers will be compared to results at the post-treatment time points described previously. Among subjects who are evidently not going to survive, or will dropout for other reasons, measures will be made immediately prior to these events, if feasible.

HEp-2 IFA are a simple Gold Standard for autoantibody detection that have been used for decades in research and clinical labs. We have described these IFA in prior studies, with corroborations by independent groups. HEp-2 IFA are also the primary endpoint of the ongoing ART-IPF trial.

In brief, commercial slides with fixed, permiabilized HEp-2 cells are incubated with plasma specimens at serial titrations from 1:20 to 1:320, along with negative control (normal IgG) and positive control standards. Plasma is washed off, and replaced with FITC-conjugated anti-human IgG, followed by fluorescence microscopy and imaging. Images are scored by **replicate blinded observers** to determine the **highest (most dilute) titer** wherein specimen

fluorescence is greater than the concurrent negative controls. **Note:** IFA for diagnoses of conventional autoimmune syndromes depend on finding specific abnormal fluorescence patterns, **whereas we use these assays to detect nonspecific patterns that are not diagnostic for SLE, scleroderma, etc**. Subjects with positive tests for known autoimmune disorders, per hospital clinical laboratories (e.g., ANA, RF, Anti-SSA, etc.), are ineligible (Exclusion Criterion #15).

B.) Anti-HEp-2 IFA Patterns: An analysis of HEp-2 IFA results to date in all AE-IPF (including the initial series treated with a less aggressive regimen[27]) indicates the pre-treatment immuno-fluorescence patterns may be associated with responses to therapy. All nine (9) AE-IPF who had nucleoli sparing (Figure 7A) responded promptly to TPE with early and significant reductions of their O_2 requirements, and their 6 month survival is 56%. In contrast, no treatment responses were evident among the five (5) patients with enhanced nucleoli staining (Fig. 7B); their median survival was 11 days, and all were dead within 6 months. The hazard ratio for nucleoli sparing vs enhanced staining is 15.2, with 95%CI = 1.7-142.9 (p=0.001). Responses were mixed, and outcomes intermediate, among the 6 AE-IPF who had neither nucleoli sparing nor enhanced nucleoli staining. Their median survivals were 23 days, and 33% were alive at 6 months.

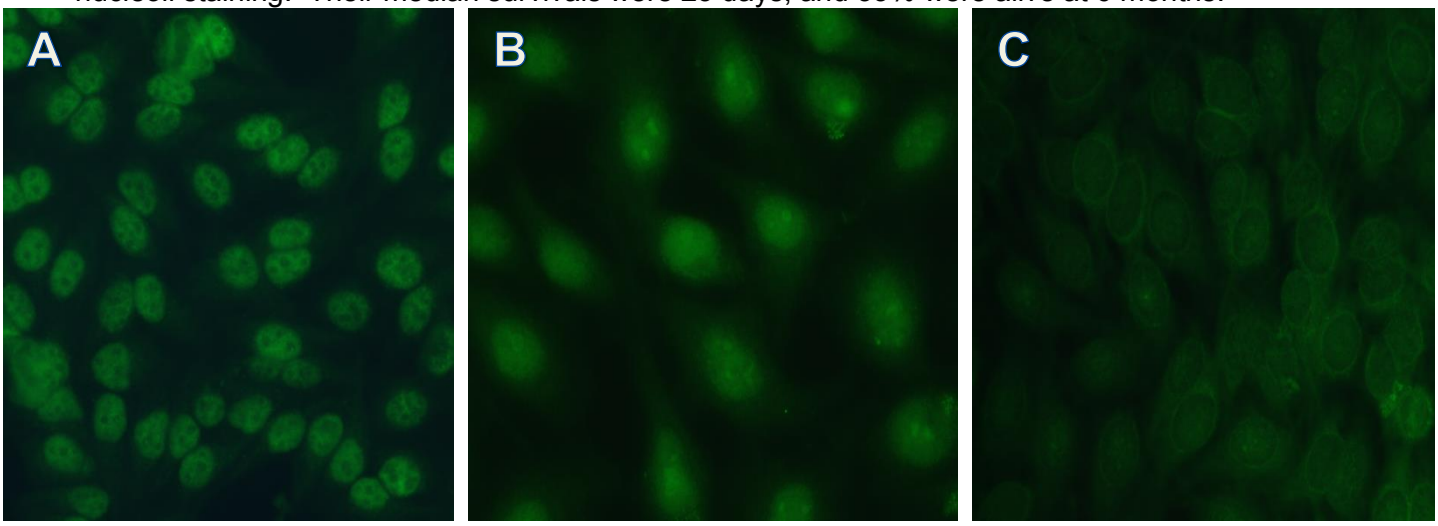


Figure 7. HEp-2 Staining Patterns of AE-IPF Plasma Specimens. HEP-2 IFA were invariably positive in AE-IPF patients, with highly varied patterns. A.) Nucleoli sparing; B.) Enhanced nucleoli staining; and C.) Other (nucleoli staining is not enhanced, and not spared. All IFA here were at 1:40 plasma dilutions.

Given these interesting preliminary results, we plan to prospectively ascertain the HEp-2 staining patterns of all subjects in both treatment arms, to test the ability of these assays to predict survival, and treatment responsiveness. Other studies now in progress will attempt to identify particular HEp-2 nucleoli autoantigens among the AE-IPF, for potential use as mechanistic biomarkers to personalize treatment

C.) Autoantibody repertoires in AE-IPF will be defined using modifications of a nonbiased discovery assay that we've previously detailed.[24] In brief, water soluble lysates are made from explanted normal lungs that were not used as donor organs.[20] We already have >20 normal lungs banked from prior studies.[20] Immunoglobulins within the lysates are removed with protein A/G, and albumin is removed by depleting resin (ThermoFisher, Rockport, IL). The lysates are adsorbed on normal IgG bound to protein G (to minimize nonspecific binding). The eluants are

next run thru columns of IPF plasma IgG covalently bound to protein G. The proteins that specifically bind to this IPF IgG (putative autoantigens) are eluted by acidification and electrophoresed on 2-D gels. Individual proteins are spot picked and sequenced by mass spectrometry (MALDI-TOF/TOF).

Three assays using **pooled plasmas** from **several stable** IPF patients have been performed.[24] Pooling was necessary given the small volumes of plasma available from individual phlebotomy specimens. HSP70 was identified in all three, along with >30 other potential autoantigens. Preliminary studies indicate several of these other identified proteins may also be autoantigens of IPF, including HSP90, HSP27, and annexin.[39]

The availability of large volume plasma specimens from the TPEs (3-5L/subject) will enable us to now determine the number and specificities of autoantibodies among **individual AE-IPF** patients.

The presence of a particular autoantibody, or panel of autoantibodies, in many or (hopefully) all AE-IPF, will be validated in homemade ELISA assays (to quantify these particular autoantibodies)[24] using plasmas from the AE-IPF subjects enrolled in this trial (phlebotomy yields are adequate for ELISA), the previously treated AE-IPF patients , and specimens collected in earlier investigations.[20-28] Prevalence(s) and concentrations (OD values) of specific autoantibodies discovered in the AE-IPF patients will be compared to findings in already collected plasma specimens from stable IPF (>200 at UPMC + UAB), >50 normal controls, and >150 COPD patients (disease controls), as detailed in prior studies. [24,28]

D.) Circulating Immunoglobulin Concentrations: Levels of IgA, IgM, total IgG and IgG isotypes will be quantified by ELISA among pre-treatment specimens and plasmas obtained 60, 90, 180, 270, and 365 days after the start of therapy. Pretreatment IgG levels could conceivably correlate with clinical responsiveness, and later measures would exclude the presence of hypogammaglobulinemia in long-term survivors. However, we do not believe IgG measures during the actual experimental therapy, or for some time thereafter (e.g., <60 days) will be helpful, since these determinations will be confounded by infusions of exogenous immunoglobulins in fresh frozen plasma (used to reverse TPE reductions of clotting factors) and the IVIG administrations during days 16-19.

E.) B Lymphocyte Stimulating Factor (BLyS, *aka* BAFF), measured by ELISA[25], may rebound after rituximab and presage clinical relapses.[62] Serial assays could find BLyS is a prognostic biomarker in treated AE-IPF patients, or indicate adjunct therapy with an anti-BlyS agent (belimumab) may be helpful in this population.

F.) Quality of Life (QoL) Measures: Patients will complete a King's Brief Interstitial Lung Disease health status questionnaire (K-BILD) at 3 and 6 months. This instrument was specifically developed for and validated in patients with interstitial lung disease, is brief, simple to administer, easy for patients to complete, measures health status in three domains, and is reproducible.[80]

2.9 DATA AND POWER ANALYSES

2.9.1 Primary Endpoint Data Analyses (6 month survival): The statistical hypothesis is:
H_0: $p_{TAU} \leq p_E$
H_A: $p_{TAU} > p_E$
Where p_E = mortality rate in the experimental arm and p_{TAU} = mortality rate in the treated as usual

arm. TAU = treatment as usual.

Baseline demographic and clinical data of participants will be summarized using means (with standard deviations) and medians (with inter-quartile ranges) for continuous variables, and counts and percentages for discrete variables, stratified by treatment group. Differences among groups (to examine the randomization effectiveness), will be assessed by t-tests, or by Fisher's exact test for discrete data. Deaths will be tabulated based on the actual day they occur, relative to the date of randomization. Survival analyses will use an exponential survival model and be summarized using Kaplan-Meier plots via product-limit estimation and log-rank tests, with **lung transplantations treated as censored events in the primary analysis**. Even though trial subjects are selected to not be eligible for lung transplants at enrollment, we anticipate some may occur, especially in the experimental arm, will improve enough to have later transplant evaluations and be listed for these procedures. Only one subject in each arm of the pilot study had lung transplants during their 6-month observations (Fig. 2). Since transplants are few and will occur relatively late, the power of our actuarial analyses will be minimally, if at all, affected.

Analysis will be based on intention-to-treat and deaths at any time will be counted against the treatment arm assigned. We expect few dropouts or cross-overs although we have budgeted for 10% dropouts in each group (see Power Analyses). TAU participants will not be permitted to cross-over to the treatment group because of the intent-to-treat analysis.

2.9.2 Primary Endpoint Power Analyses: A one-sided log-rank test with an overall sample size of 51 subjects (17 in the control group and 34 in the treatment group) achieves 97.6% (94.6% two-tailed) power at a 0.05 significance level to detect a hazard ratio of 0.3 when the control group hazard rate is 1.00. The subject accrual (entry) occurs over 40 months. The accrual pattern across time periods is assumed to be uniform (all periods equal). The proportion dropping out of the control group is 0.10. The proportion dropping out of the treatment group is 0.10. The proportion switching from the control group to another group with a hazard rate equal to the treatment group is 0. The proportion switching from the treatment group to another group with a hazard rate equal to the control group is 0.

2.9.3 Interim Analysis: A formal interim analysis for safety as required by the DSMB will occur when 30/51 = 59% of the overall study information should be available, approximately 6 months after the 30th patient is randomized. The safety analysis will be based on serious adverse events, as defined by the NCI Common Toxicity Criteria Scale, that are treatment-related or possibly treatment-related, as well as AE-IPF relapses. Other adverse events of lesser severities, and/or not directly related to the treatments, are also routinely recorded per protocol, and will provide additional information for consideration by the DSMB at the interim analysis. The formal interim safety analysis will be conducted when 30 patients have completed treatment (20 experimental and 10 controls) using a lower boundary of a nominal 0.05 level with no adjustments for Type I errors since this is a safety assessment. The DSMB will monitor the incidence of mortality in the cohort and no formal stopping rules are proposed for mortality. More precisely, adverse event rates between groups will be compared by employing negative binomial regression (proc genmod procedure in SAS) and person months of exposure will be used as an offset variable to control for unequal exposure time (i.e., time to death and/or relapse). The 6 month adverse event rate will be assessed using the person months of exposure concept, since it is expected that there will be greater mortality in the TAU group and thus, unequal exposure times will need to be controlled. We will continue to enroll participants during the period while the safety interim is being conducted, but if a safety signal is observed, the DSMB will decide the benefit versus risk of continuing. If there is a safety

difference at the interim analysis that reaches nominal statistical significant, the DSMB may consider stopping the trial, depending on the direction and the outcome of mortality after examining all evidence, including overall safety and efficacy.

2.9.4 Secondary Endpoint Data Analyses: O_2 requirements and six minute walks will be assessed immediately prior to treatment and after completion of therapy on day 19, as well as on days 60, 90, 180, 270, and 365. Subjects discharged from the hospital after completion of the protocol will be instructed to return to our clinics for these scheduled assessments. These visits, visit intervals, and actual endpoint measures are already standard of practice in our IPF clinics. Adverse events and relapses that occur anytime during the subjects participation in this study will be recorded and compared (Table 4).

	Baseline	Day 19	Day 60	Day 90	Day 180
O_2 Required	X	X	X	X	X
6MWD	X	X	X	X	X
Adverse events	---Anytime----				
Relapses	---Anytime----				

Table 4. Schedule of secondary endpoint assessments. Tabulations of adverse events will occur not only on those scheduled times denoted here, but will also include any adverse events that have occurred at intervals in between those visits.

Although each participant's formal involvement with the study lasts 6 months (180 days), we intend to continue to collect periodic data on these patients at their subsequent routine and standard medical visits (e.g., at 270 and 365 days after the start of treatment), Based on observations to date, we believe the majority of those subjects who had clinical benefits evident at 6 months will continue in remission for a more prolonged, if as-of-yet undefined, period. Thus, additional longitudinal observations after treatment will help us to determine the practical duration of treatment effects. These data will, in turn, be invaluable to develop subsequent maintenance regimens (and/or design follow-on studies) that could optimize the care of AE-IPF patients.

We anticipate many TAU subjects will deteriorate **rapidly, and secondary endpoint** measures will often be infeasible at later time points. Nonetheless, the analyses proposed here will still enable early intergroup comparisons that will confirm treatment effects. Later measures (probably mostly among surviving experimental arm subjects) will provide information about the durability of therapy. Analyses will follow intention to treat principles.

For the secondary analyses, we will use repeated measures mixed effects models to utilize the maximum data from each participant, in addition to the dichotomized (improved vs. otherwise) assessments for oxygen requirements and walk distance (to follow). The proportion of subjects with significant O_2 and 6MWD changes in each arm will be compared by Fisher's exact test. For sensitivity analyses, we will use the worst O_2 from a completing patient for any deaths within each treatment group. Similarly for the 6 minute walk we will impute the worst time within the treatment arm surviving to complete the walk. For the AEs and Relapses, we will use Poisson regression with an offset for the time under study.

2.10 DATA COORDINATING CENTER (DCC):

The DCC, under the direction of Dr. Fazlur (Co-Invest), will be responsible for data management and analyses. The DCC includes experienced research methodologists and data base managers, in addition to data and IT support staff (see also Resources and Facilities). The DCC

will provide full service electronic data capture, participant tracking, automated SAE notification, QA/QC reporting, other study reports and data management services with a secure password protected system that is consistently backed up. The extent of these data management services include: database specification, edit check programming, management plan development and maintenance, ongoing manual data review and query management, medical coding and data cleaning and locking. Serving as the repository of all study data collected, the DCC will interface with the various investigators for their specialized data and results. The DCC will also provide programming, statistical analysis and medical writing services, which include the programming of data summaries, tables, and statistical analyses. The DCC will also provide requested data to the DSMB and assist with the interim monitoring meeting(s), study progress tracking, and safety monitoring. In addition, the DCC will be responsive to requests from the IRBs at the clinical sites or the NHLBI.

Each clinical site will be audited to assure that they are collecting data and treatment is being provided in accordance with the protocol. Audits of a random selection of data, and all protocol consents will also be reviewed. A report will be sent to the Clinical Sites, DSMB, and NHLBI after each site visit.

2.11 ANTICIPATED RESULTS AND PITFALLS

2.11.1 Specific Aim 1 (Primary Endpoint).

Anticipated Results and Potential Pitfalls: We predict survival will be greater in the experimental arm (Fig. 2).

Insertion of large bore dialysis (TPE) catheters has risks and discomforts. We chose not to have a placebo arm since insertions in TAU controls for no benefit (these are NOT routinely used for i.v. infusions) may be problematic for subject recruitment. Further, TPE is dynamic (blood in; blood out; plasma out; albumin in, etc.), and the machine is large, complex, and does not have sham provisions. Many patients will be too ill to safely transport for non-essential reasons. We cannot devise a way to blind observers, staff and TPE techs. Thus, this study is unblinded. Inadvertent bias should be minimal, however, given the unequivocal primary endpoint.

It is possible, albeit unlikely, the benefit of TPE in AE-IPF could be due to removal of mediators other than autoantibodies. However, we found plasma levels of matrix metalloproteinase 7 (MMP7), an enzyme involved in degradation of extracellular matrix, and a representative soluble mediator of IPF, were not associated with TPE, or clinical responses.[27] Furthermore, the duration of TPE effects on soluble factors is limited.[17,18] and cannot readily account for the prolonged remissions of several trial subjects (Fig. 2).

The experimental regimen is unlikely to reverse the lung fibrosis that afflicted these patients prior to their AE. Nonetheless, easing symptoms and prolonging survival is a worthwhile goal, and a focus of much effort in other serious diseases (e.g., oncology, pulmonary artery hypertension, etc). Moreover, prolonging survival will enable patients to have transplant evaluations, and live long enough to procure a donor organ.[27]

The duration of a single treatment course will almost certainly be finite, although several subjects have had prolonged remissions (Fig. 2, see also[27]). Patients with other autoantibody diseases who respond to analogous therapy may get consolidation therapy to sustain their remissions. We do not believe consolidation therapy can be incorporated into this trial. The **first principle**

here is to assess benefits of autoantibody-targeted therapy. If so, later trials can focus on further prolonging remission durations with consolidation therapies (if necessary). Proposing a consolidation now, prior to first proving our hypothesis, is premature, and would require a complex trial design with more subject groups (**and <u>much larger</u> "n"**).

2.11.2 Specific Aim 2 (Secondary Endpoints) Anticipated Results and Pitfalls

O_2 need assessments and 6MWD are simple and standard of practice (SOP) in our medical centers. Our dichotomous categorizations will highlight <u>clinically relevant</u> treatment effects (with practical meanings for patients) as opposed to lesser (and perhaps even trivial) simple mathematical changes. The large changes necessary to qualify as treatment effects here are also more reliably tabulated, and less subject to unintentional bias than entry of small interval values. A potential downside is loss of power (given dichotomous rather than continuous variable comparisons), but after witnessing therapy effects, we anticipate treated subjects will more often show large endpoint improvements, compared to TAU (Fig. 1).

Serial measures up to 1 year after treatment will help us determine <u>duration of effects</u>, as we anticipate many experimental arm subjects will be remission-free for >6 months (Fig 2. and citation[27]). Many TAU subjects will likely deteriorate, and their secondary endpoint measures will often be infeasible at later time points. Nonetheless, analyses of the early time points will still enable us to prove <u>treatment benefits</u>.

Based on multiple studies involving thousands of patients treated with analogous regimens, and our experiences (Figs. 1, 2),[27] we anticipate adverse events will not be significantly greater among experimental arm subjects, and the trial regimen will have an acceptable risk:benefit ratio in these high-risk patients.

Based on experiences to date, we anticipate a greater proportion of TAU patients who improve and are discharged from their initial hospitalization will have relapses, compared to experimental arm subjects.

2.12 STUDY TIMELINES AND MILESTONES

<u>Timelines and Milestones</u>: Infrastructure and regulatory requirements should be completed by <u>≤</u>9 months after funding is awarded (Figure 8). This consortium has considerable clinical trial experience. Our clinical experience with this therapy will let us "hit the ground running". Our creative plan for funding patient care costs enables us to study many more subjects at many more centers than if the NIH had to assume the entire financial burden (see Budget Justification). Our potential subject population is greater than the necessary study numbers that we will easily meet this conservative target enrollment, and assuming reasonable consent, we anticipate doing so ahead of schedule, which would save even more money (see Feasibility- above).

	Year 1			Year 2			Year 3			Year 4			Year 5		
Month:	**1-4**	**5-8**	**9-12**	**1-4**	**5-8**	**9-12**	**1-4**	**5-8**	**9-12**	**1-4**	**5-8**	**9-12**	**1-4**	**5-8**	**9-12**
Regulatory and Logistic															
Subject Enrollment (n)			5	5	5	5	5	5	6	6	6	3			
Data Analyses															

Figure 8. Projected timeline and milestones, relative to the Notice of Award date.

3 HUMAN SUBJECTS

3.1 SUBJECT POPULATION

Human Subject Characteristics:
Fifty-one (51) adult IPF subjects with acute exacerbations of their lung disease, of both genders and all ethnic backgrounds, who are hospitalized at any of the four participating medical centers, will be eligible for enrollment. Subjects must provide written informed consent prior to participation. Surrogate consent will not be allowed. No special vulnerable populations will be studied.

Participating Centers:
Each participating center is expected to comply with appropriate regulatory, protocol, and data collection requirements.

1. University of Alabama at Birmingham (UAB).
2. Brigham and Women's Hospital (BMH) -No Longer Active
3. Temple University Hospital (TUH)
4. University of Pittsburgh Medical Center (UPMC)
5. Baylor University (BU)
6. University of Utah (UU)
7. Thomas Jefferson University (TJU)

The study-specific identifying numbers for these centers are:

01 (UAB)
02 (BWH)
03 (TUH)
04 (UPMC)
05 (BU)
06 (UU)
07 (TJU)

Clinical Coordinating Center (CCC):
The Clinical Coordinating Center and the Lead Institution is UAB. The CCC will be responsible for coordination, development, and monitoring the submission, and approval of the protocol and consent documents, as well as any subsequent amendments per the individual institution IRB's and applicable regulatory guidelines. The CCC will ensure that all participating centers in the multi-center protocol demonstrate their intent and capability of complying with Federal Regulations, Good Clinical Practices (GCP) and HIPAA requirements.

3.1.1 Inclusion of Women and Minorities

Women who meet the inclusion criteria, and have none of the exclusion criteria, will be enrolled without restriction as dictated by the study protocols. Because of the use of a study medication, woman of child bearing potential must meet specialized inclusion/exclusion criteria to minimize this risk. We will make efforts to enroll participants in this research in a distribution which mirrors the study populations of the participating medical centers.

3.1.2 Inclusion of Children

Children under 18 years of age will not be enrolled because they do not develop this disease.

3.2 INCLUSION AND EXCLUSION CRITERIA

The inclusion criteria have been selected to isolate a patient population with idiopathic pulmonary fibrosis with acute disease exacerbations. The exclusion criteria are selected to not enroll patients with an alternative cause for a respiratory decompensation and to exclude patients with increased risk for the associated interventions.

Inclusion Criteria

1.) Age between 40-85 years old.

2.) A diagnosis of IPF that fulfills ATS/ERS Consensus Criteria.[1]

3.) Hospitalized patient with a diagnosis of AE-IPF, as ascertained by the responsible Primary Investigator, with findings that include worsening or new development of dyspnea or hypoxemia within the last 30 days.

4.) Ground-glass abnormality and/or consolidation superimposed on a reticular or honeycomb UIP pattern on locally read chest CT scan.

5.) Ability and willingness to give informed consent and adhere to study requirements.

Exclusion Criteria:

1.) Diagnoses of current infection per clinical or microbial assessments.

2.) Diagnoses of an additional or alternative etiology for respiratory dysfunction based upon clinical assessment, including congestive heart failure, sepsis, thromboembolism, etc,

3.) History or serological evidence of hepatitis B, or current hepatitis C infection.

4.) Coagulopathy, defined as an INR >1.6, PTT > 2x control, fibrinogen <100 mg/dL, or platelet count <50K unless these abnormalities can be reversed safely.

5.) Hyperosmolar state or diabetic ketoacidosis to suggest uncontrolled diabetes, or uncontrolled hypertension (systolic BP >160 mm Hg and diastolic BP >100 mm Hg) that would contraindicate use of corticosteroids.

6.) Hemodynamic instability, defined as an inotrope or vasopressor requirement.

7.) History of reaction to blood products or murine-derived products.

8.) Active malignancy or undergoing treatment of malignancy, excluding basal or squamous cell skin cancer and low-risk prostate cancer, the latter defined as stage T1 or T2a, with prostate specific antigen (PSA) less than 10 ng/dl. The experimental treatments are not known to promote cancer progression, and these criteria are within current guidelines.

9.) Unwillingness to accept blood product transfusion.

10.) Diagnosis of major comorbidities, or other considerations, that the responsible physician-investigators believe should disqualify subjects, or are expected to interfere with study participation.

11.) Treatment for >14 days within the preceding month with >20 mg. prednisone (or equivalent) or any treatment during the last month with a cellular immuno-suppressant (e.g., cyclophosphamide, methotrexate, calcineurin inhibitors, mycophenolate, azathioprine, etc.). An exception will be made if the patient has a bronchoalveolar lavage (BAL) negative for pathogens.

12.) Presence of a condition or ongoing treatment with a medication that precludes TPE.

13.) Concurrent participation in other experimental trials.

14.) Fertile females who do not agree to contraception or abstinence, or have a positive pregnancy test (urine or blood). IPF is a disease of older adults, and male predominant, so this will not be a frequent consideration.

15.) Presence of positive (abnormal) classical autoimmune tests: ANA, RF, Anti-SSA, and Anti-CCP. This criterion will eliminate patients with confounding classical autoimmune syndromes. Many IPF patients will have already had these tests, which are standard of practice (SOP) at many IPF centers, and these prior results will suffice if the tests were performed within the last year. Otherwise, these tests need to be performed prior to enrollment and they can usually be procured in 1-2 days. ANCA will continue to be tested during screening but negative results are no longer a requirement for randomization. Based on experience, we anticipate ~10% of patients who fulfill all other IPF criteria will nonetheless be positive for one of these classical autoantibody tests.

16.) IgA deficiency (IgA level <7 mg/dL)- to preclude IVIG reactions.

17.) Listed with the United Network for Organ Sharing for lung transplant <u>at the time of enrollment</u>.

18.) Patients who are intubated at time of STRIVE enrollment.

19.) Prior use of rituximab within the year preceding enrollment.

20.) Clinical or Morphologic Domain criteria of IPAF.[2]

Clinical Domain Criteria include: distal digital fissuring (i.e., "mechanic hands"), distal digital tip ulceration, inflammatory arthritis or polyarticular morning stiffness >60 min, plamar telangiectasia, Raynaud's phenomenon, unexplained digital edema, unexplained fixed rash on the digital extensor surfaces (Gottron's sign).

Morphological Domain Criteria include: any radiographic or histopathological finding other than UIP (e.g., NSIP, LIP, etc.), or multi-compartment involvement of unexplained pleural or pericardial effusions or thickening.

3.3 INFECTIOUS CONSIDERATIONS

<u>Infectious Considerations</u>: AE-IPF is infrequently complicated by occult bacteria or viral pulmonary infections and, in the absence of treatment with cellular immunosuppressants, **rarely** (if ever) complicated by occult opportunists.[1-7] BAL are **not SOP** prior to administration of rituximab to autoimmune populations, many of whom have lung diseases that resemble IPF.[5-18] Invasive diagnostic procedures to exclude occult pulmonary infection are also **<u>not SOP</u>** for AE-IPF evaluations at our hospitals due to the rarity of infections, poor diagnostic yields, and

potential risks. A detailed review of 35 AE-IPF admissions to UPMC revealed that BAL was performed in only 9 (26%), was uniquely productive in only 2 (6%), and our SOP antibiotic regimen covered those organisms. Most subjects will have tenuous respiratory function at entry,[27] and BAL or TTA will result in gratuitous intubations, while providing questionably useful data. All physician investigators believe that requiring mandatory invasive procedures for AE-IPF subjects is contraindicated, and refuse to participate if this becomes an enrollment criterion. Instead, procedures will be performed in potential subjects **when they are safe and are indicated in the judgment of the attending physician.**[27] However, potential subjects recently treated with immunosuppressants MUST have a prior negative BAL (Exclusion Criterion #15). Rituximab **decreases autoantibody titers**, but total immunoglobulins are less reduced (if at all). Infection rates after rituximab therapy are minimally if at all different than those of placebo controls TPE only transiently reduces immunoglobulins, and is not usually associated with serious infections. Potential effects of TPE and rituximab on immunoglobulins should also be mitigated by IVIG therapy.

Given the ongoing profusion of highly sensitive viral detection assays, which in many cases have unspecified clinical significances, the putative identification of a virus in respiratory or other specimens among potential subjects will need to be interpreted by attending and study physicians in the appropriate clinical context. As an example, the identification of a rhinovirus in a nasal swab may have triggered the AE-IPF, but seems unlikely (given current information) to primarily account for the pulmonary infiltrates and respiratory compromise. On the other hand, the frequent association of influenza (A and B), adenovirus, and respiratory syncytia virus (RSV) with pulmonary disease will exclude recruitment of AE-IPF patients who have positive tests for these viruses. Other viral identifications with questionable significance in non-immunocompromised patients (e.g., parainfluenza, metapneumovirus) will be considered on a case-by-case basis.

4 RECRUITMENT AND INFORMED CONSENT PROCEDURES

4.1 RECRUITMENT METHODS

Subjects will be recruited from the inpatient population among the participating institutions. The primary care physician/clinical care team, who may be study investigators or colleagues of the study investigators, will first identify potential research subjects. The clinician investigators will discuss the research project with the potential subjects.

4.2 INFORMED CONSENT PROCEDURES

The consent process will begin via one of two possible pathways:

1) Referral of the prospective participant to the investigators/research coordinator by a physician who has knowledge of the proposed research, and obtains patient consent for the research team to approach the patient/surrogate.

2) Individuals who have provided signed IRB-approved HIPPA compliant consent for participation in clinical trial research registries.

Subjects must provide informed consent prior to performing any of the study procedures. The information about this study will be given to subjects in language understandable to subjects. Only physician investigators will present the study to the potential subjects. The physician investigator will verbally present a general outline of the research plan, including inclusion and

exclusion criteria, to the prospective participant. The consent form, outlining the design of the study, will include the risks and benefits of participating, and will be reviewed and the investigator will answer any questions. Prospective participants may take as much time as required to make an informed decision. Written informed consent will be obtained from each participant prior to performing any research study procedures.

In addition, older potential study participants whose competency to consent is in question will be tested for sufficient comprehension and recall of the information presented. Prospective subjects who do not remember the important facts about participation in the research study after repeated testing will not be included in the study. The investigators will also assess whether a participant understands experimental procedures over time, including assessment throughout the full duration of participation in the study.

5 POTENTIAL RISKS AND BENEFITS

5.1 POTENTIAL RISKS

5.1.1 General Risks of Study Protocol and Procedures

The potential subject risks specifically related to the study protocol procedures could include loss of confidentiality or actual physical harm due to experimental procedures.

5.1.2 Potential Risks of Experimental Intervention

The potential subject risks specifically related to the study protocol procedures could include:

Insertion of a central venous catheter for plasma exchange:
Common Risks: Bleeding at the insertion site, pneumothorax, catheter-associated blood clots, internal hemorrhage/hemothorax, and infections.

Plasma Exchange:
Common Risks: A drop in blood pressure that may be associated with symptoms of dizziness or light-headedness, and mild/transient citrate toxicity (perioral tingling or numbness, paraesthesia, nausea, vomiting).

Other Risks: Unusual complications include extracorporeal anticoagulation, severe hypocalcemia leading to muscle irritability, cardiac arrhythmias, and seizures, infections by blood products (plasma and/or cryoprecipitated AHF), transfusion reactions, allergic reactions to the replacement solutions or sterilizing agents for the tubing, and adverse effects of immunosuppression produced by the associated hypogammaglobulinemia (although this will be mitigated by the IVIG therapy).

Corticosteroid (methylprednisolone- premedication for rituximab):
Common Risks: Insomnia, nausea, vomiting, upset stomach; fatigue or dizziness; muscle weakness or joint pain; problems with diabetes control; or increased hunger or thirst. Nonetheless, corticosteroids are SOP for acute exacerbations of IPF, despite an absence of supporting data.

Other Risks: Acne, increased hair growth, thinning of the skin, cataracts, glaucoma, osteoporosis, roundness of the face, and changes in behavior.

Rituximab:
Common Risks: Fever, chills, headache, pain, rash, pruritus, angioedema, nausea, abdominal pain, cytopenias, weakness, cough, rhinitis. Infusion related reactions: angioedema, bronchospasm, chills, dizziness, fever, headache, hyper-/hypotension, myalgia, nausea, pruritus, rash, rigors, urticaria, and vomiting.

Infrequent Risks: Hypotension, peripheral edema, hypertension, flushing, edema, dizziness, anxiety, agitation, depression, hypoesthesia, insomnia, malaise, nervousness, neuritis, somnolence, vertigo, migraine, urticaria, hyperglycemia, hypoglycemia, hypercholesterolemia, diarrhea, vomiting, dyspepsia, anorexia, weight loss, anemia, pain at the injection site, back pain, myalgia, arthralgia, paresthesia, arthritis, hyperkinesia, hypertonia, neuropathy, conjunctivitis, lacrimation disorder, throat irritation, bronchospasm, dyspnea, upper respiratory tract infection, sinusitis, LDH increases.

Other Risks: Rare events associated with rituximab include severe mucocutaneous reactions, progressive multifocal leukoencephalopathy due to LC virus reactivation, hepatitis B reactivations, and other infections.

Intravenous Immunoglobulin (IVIG):
Serious risks include renal insufficiency, venous or arterial thrombotic events, and anti-IgA-mediated anaphylaxis. Adverse events in >5% of subjects include headache, chills, fever, shaking, fatigue, malaise, anxiety, back pain, muscle cramps, abdominal cramps, blood pressure changes, chest tightness, palpitations, nausea, tachycardia, vomiting, cutaneous reactions, wheezing, rash, arthralgias, and edema.

Venipuncture:
Common Risks: temporary, minor discomfort, bruising.

Other Risks: infection, bleeding and phlebitis.

5.2 ALTERNATIVE TREATMENTS

The alternative treatments for the subjects participating in this investigation are to continue their TAU medical care under the direction of their attending physician.

5.3 POTENTIAL BENEFITS

Participation in the proposed research may or may not provide a direct benefit to the subjects. Potential benefits from the participation in this protocol include enhanced survival, improved respiratory symptoms, and decreased exacerbation severity. Identification of the mechanism(s) mediating these outcomes will facilitate risk-stratification for these adverse outcomes, and development of targeted treatment strategies for the future.

Based on the preceding assessment of risks and potential benefits, the risks to subjects are reasonable in relation to anticipated benefits. The research presents a balance of risks and expected direct benefits similar to that available in the clinical setting.

Importance of the Knowledge to be Gained

The preliminary data in this application outline a hypothesis for the progressive clinical deterioration in patients with acute IPF exacerbations. The protocol specifically seeks to address that hypothesis. If the study intervention is found to be both safe and effective in the study population, the treatment of IPF would be altered significantly, and ultimately could lead to a change in the disease natural history. Completion of these protocols will begin to address important questions related to disease.

5.4 DATA SAFETY MONITORING PLAN

5.4.1 Data Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB), independent of the study investigators, will monitor the clinical trial outlined in this proposal for the duration of this proposal. The DSMB will be appointed by the sponsoring agency (NHLBI), from among experts in the field. The Food and Drug Administration has already provided an exemption from IND requirements for this protocol. Each participating site will complete local Institutional Review Board (IRB) approval. The specifics of the DSMB structure and function are outlined below.

The DSMB will be expected to meet as needed, but not less than every six months, to review the progression of the study including patient enrollment, protocol compliance, and adverse event reports. The DSMB will conduct interim monitoring of accumulating data from research activities to assure the continue safety of human subjects, relevance and appropriateness of the study, and the integrity of research data.

5.4.1.2 Clinical Coordinating Center (CCC)

The CCC is the UAB study team, led by the Contact PI and the Protocol Chair, Dr. Steven Duncan. The CC will ensure that all participating institutions within the multi-center protocol demonstrate their intent and capability of complying with Federal Regulations, GCPs and HIPAA requirements.

Each study site will be subject to on-going monitoring. Study sites will be evaluated for meeting enrollment criteria and for the accurate and timely submission of data forms, and timely response to data queries from the study monitors or data coordinating center.

The UAB study team will assume the following general responsibilities:

- Assist in protocol review.
- Maintain copies of FWA and Institutional Review Board (IRB) approvals from all Participating Institutions.
- Maintain updated roster of participants.
- Verify eligibility.
- Verify response.
- Collect data on protocol specific CRFs.
- Prepare all submitted data for review by the Protocol Chair.
- Maintain documentation of Serious Adverse Event reports submitted by Participating Institutions and submit to Protocol Chair for timely review.
- Distribute Serious Adverse Event safety reports.
- Monitor participating institutions either by on-site inspection of selected participant records and/or with source documents and research records submitted to the Coordinating center.

5.4.1.3 Data Coordination Center (DCC)

The DCC will provide methods for data entry, management, quality control, and analyses, and provide administration and maintenance of a comprehensive database. The DCC, based in the UAB Department of Biostatistics in the School of Public Health, is directed by Dr. Rahman Fazlur (Co-Investigator). The School of Public Health is adjacent to the UAB Hospital complex.

In conjunction with the clinical trial PIs, the DCC will establish a data collection protocol and mechanism. Data will be collected on paper Case Report forms. The data on these forms will then be entered into a database at the Clinical Site by manually typing the data into the database, through the Web-based system. All data are loaded into a central database and can be managed using the online data management system. Numerous data quality checks, such as duplicate entry checks, double-entry verification, and real-time data checking (e.g., ID verification, range checks) will be implemented to ensure that the data are accurate, complete and secure. Data entry personnel will be trained and certified in the correct use of the system.

5.4.1.4 Participating Institutions

Each Participating Institution will provide to the CCC a list of the key personnel assigned to the role for oversight of data management at their site. The general responsibilities for each Participating Institution are as follows:

- Commit to accrual to the multi-center protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain a regulatory binder.
- Update Coordinating Center with research staff changes on a timely basis.
- Submit source documents, research records, and CRFs per protocol specific submission guidelines to the CCC.
- Submit Serious Adverse Event reports to local IRB and provide copies to the CCC.
- Submit deviations and violations to their local IRB and the CCC.

5.4.1.5. Adverse Events: The National Cancer Institute Common Toxicity Criteria Scale will be used to define grades (severity) of adverse events and toxicities. An adverse event is any untoward medical occurrence in a participant who received study drug, regardless of its relationship to the study drug. Toxicity is an adverse event with a direct relationship to the study drug. All toxicities are adverse events, but not all adverse events are toxicities. This is a determination made by the study investigator. The study investigators will classify adverse events as “definitely", "most likely,” “possibly,” “unlikely” or "clearly not" due to the study drug. Toxicity will be defined as an adverse event that is definitely, most likely, or possibly caused by a study drug or procedure.

The severity of adverse changes in physical signs or symptoms will be classified as follows:

- Grade 1 (Mild): asymptomatic or mild symptoms; clinical or diagnostic observation only; intervention not indicated.

- Grade 2 (Moderate): minimal, local or noninvasive intervention indicated; limiting age-appreciate instrumental ADL (Activities of Daily Living).

- Grade 3 (Severe): medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

- Grade 4 (Life-threatening): consequences; urgent intervention indicated.

- Grade 5 (Death): event is a direct cause of death.

Assuring patient safety is an essential component of this protocol. The contact PI has primary responsibility for the oversight of the data and safety monitoring. The study investigators will evaluate all adverse events. All subjects who have adverse events, whether considered associated with the use of the study medication or not, must be monitored to determine the outcome.

The study coordinators must view patient records for possible adverse event on a daily basis, while subjects are hospitalized. All untoward medical occurrences observed in subjects will be recorded on the participants' adverse event case report forms (CRF) by the study coordinator under the supervision of the PI, with a particular focus on infections (including location and organism), catheter-related problems (e.g., bleeding, clot), apheresis-related complications (e.g., hypotension, citrate toxicity, etc), metabolic or hemodynamic perturbations (e.g., hyperglycemia, hypotension, etc.) and other, less frequent complications (e.g., neurologic symptoms), as well as having provision for free text entries. Recording all adverse events in pre-specified checklists (and free text entries), will guard against unintended bias. The CRFs will then be reviewed for completeness and internal consistency. Subsequently, the CRFs will be recorded on an electronic password-guarded study database. In addition to internal safeguards built into a computerized system, external safeguards will be put in place to ensure that access to the computerized system and to the data is restricted to authorized personnel. Training conducted by qualified individuals on a continuing basis will be provided to individuals in the specific operations with regard to computerized systems that they are to perform during the course of the study.

The clinical course of the adverse event will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the PI considers it medically justifiable to terminate follow-up.

The contact PI will work with the reporting investigators and DCC to prepare a detailed written summary of serious, unexpected, and treatment related adverse events, and will compare, and contrast the event with prior events. The detailed written summary will be provided to the DSMB and the IRB.

In addition, the DSMB Report addressed the following information will be submitted to the IRB at the time of continuing review annually or more often as required:

- A list of the research personnel who participated in the data and safety monitoring.

- The frequency of monitoring that took place during the renewal intervals and/or the dates that data and safety monitoring was conducted.

- A summary of cumulative data related to unanticipated problems (including adverse events) including a determination of causality and whether the risk to benefit assessment has changed.

- If appropriate, a summary of pertinent scientific literature reports, therapeutic

developments, or results of related studies that may have an impact on the safety of study participants or the ethics of the research study.

- A summary of the outcome of reviews conducted to ensure subject privacy and research data confidentiality.

- Final conclusions regarding changes to the anticipated benefit-to-risk assessment of the study participation and final recommendations related to continuing, changing, or terminating the study.

5.4.2 STOPPING RULE:

Individual subject specific stopping rules:
A study participant will be discontinued from further study drug treatment/Intervention(s) administration if any of the following occur:

- Any clinical adverse event, laboratory abnormality, intercurrent illness, other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- Development of any exclusion criteria may be cause for discontinuation (eg: hemodynamic instability, defined as a vasopressor requirement that would contraindicate the use of plasmapheresis).
- Intercurrent illness or an unexpected fatal or life-threatening adverse event, which requires discontinuation of study treatment
- Request by the subject to withdraw from the study
- Investigator discretion

5.4.3 Trial Termination due to Efficacy or Inefficiency: See Section 2.9.4.

5.4.4 Parameters to be Monitored
The following progress will be monitored throughout the course of the research to ensure the safety of subjects as well as the integrity and confidentiality of their data.

- An evaluation of the progress of the research study, including subject recruitment and retention, and an assessment of the timeliness and quality of the data.

- A review of collected data (including adverse events, unanticipated problems, and subject withdrawals) to determine whether there is a change to the anticipated benefit-to-risk assessment of study participation and whether the study should continue as originally designed, should be changed, or should be terminated.

- An assessment of external factors or relevant information (eg. Pertinent scientific literature reports or therapeutic development, results of related studies) that may have an impact on the safety and study participants or the ethics of the research study.

- A review of study procedures designed to protect the privacy of the research subjects and the confidentiality of their research data.

5.4.5 Frequency of Monitoring

The contact PI will review subject safety data as it generated. The principal investigators, co-principle investigators, and the research staff will meet or converse bi-monthly when the study is being initiated, and then thereafter at least at monthly intervals, or more frequently if necessary, to re-evaluate study goals, subject recruitment, data coding and retention, documentation and identification of adverse events, complaints, and confidentiality of subjects. There will be an evaluation of the progress of the research study, including assessments of data quality, time lines, participant recruitment, accrual, and retention. The PIs will also review the outcome and adverse event data to determine whether there is any change to the anticipated benefit-to-risk ratio of study participation and whether the study should continue as originally designed or should it be re-evaluated and changed.

The DSMB is expected to meet as needed, but not less than every 6 months, to review the progression of the study including patient enrollment, protocol compliance, and adverse event reports. An emergency meeting of the DSMB may be called at any time by the Chair should participant safety questions or other unanticipated problems arise.

5.4.6 Reportable Adverse Events

For this study, a **Serious Adverse Event** is any untoward clinical event that is thought by the responsible investigator to be study-related, that is also:

1. Fatal or immediately life threatening
2. Permanently disabling, or severely incapacitating.
3. Requires, or prolongs, inpatient hospitalization.
4. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient, or subject, and may require medical, or surgical intervention to prevent one of the serious outcomes listed above.

If clinically important and unexpected adverse experiences, or clinically important study-related adverse experiences occur, they will be recorded on the adverse event case report form.

5.4.7 Adverse Events Reporting Timeline

The investigators will report life-threatening or fatal unexpected adverse events associated with the use of the study drug or procedures to the contact PI, DCC, NHLBI, DSMB, the local IRB, and central IRB (for the CCC) within seven (7) calendar days of discovery of the incident

Serious (but not fatal or life-threatening) and unexpected adverse events associated with the use of the study drugs or procedures must be reported to the DCC, NHLBI, DSMB, the local IRB, and central IRB (for the CCC) within 15 calendar days.

5.5 RISK MANAGEMENT PROCEDURES

5.5.1 Protection Against Loss of Confidentiality

All research interventions/activities will be conducted in private patient care areas. The collection of sensitive information about subjects is limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected.

To avoid any violation of subject confidentiality, all data will be stored in a password-protected database, identified only by study ID number at the DCC. A confidential database linking patient identifying information with study ID number will be maintained at each clinical site; the CCC or DCC will not be in possession of patient identifying information.

All demographic and clinical information about the subject will be stored on an electronic password-guarded study database under the supervision of the PIs for this protocol. All staff will sign confidentiality statements. Access to the database will be limited to the data manager and staff under the supervision of the PIs.

Specimens will be stripped of subject identifiers and stored according to a similar coding protocol as described above. These specimens will be stored safely in the custody of the Principal Investigator responsible for the individual assays. These Investigators will limit future access to any remaining sample to only those investigators with prior IRB approval for their studies.

The PIs will retain the data for the entire period of this study. The investigators may continue to use and disclose subjects de-identified information for the purpose of this study for a minimum of seven years after final reporting or publication of the study. If the subject and/or legal representative decide to withdraw or be withdrawn from study participation, they may request that the study data and samples be destroyed.

All staff involved in this study are properly credentialed and instructed in the areas of testing, confidentiality, and safety. All principal and co-investigators, coordinators, and other Key Personnel are required to participate in courses and be certified as mandated by local IRBs regarding Education and Certification Programs in Research & Practice Fundamentals (RPF).

5.5.2 Protection Against Potential Risks of Experimental Intervention

Despite the documented safety profile of plasma exchange, rituximab, and IVIG in other human disorders of abnormal immune regulation, the study has been designed with a focus on protecting patients against risk including:

Selection of a target patient population with a very high risk of morbidity and mortality due to the absence of a defined treatment for the disorder.

Involvement of trained staff in central venous access placement for the provision of plasmapheresis and utilization of ultrasound guidance for placement of all catheters
Involvement of trained hospital staff for the provision of plasmapheresis in patients with advanced medical illness

Involvement by trained staff / investigators with experience in the administration of Rituximab

Prior human experience with the study medication in similar conditions with an autoimmune hypothesis including rheumatoid arthritis and myositis

Exclusion of all patients with conditions which might simulate IPF exacerbations such as congestive heart failure, pneumonia, and pulmonary thromboembolism

Continuous monitoring by an independent DSMB

Particular Risk Mitigations for:

Therapeutic Plamsa Exchange: The subjects will undergo routine monitoring of coagulation parameters (fibrinogen) with correction of acquired defects during the procedure consistent with existing medical practice. Patients with contraindications to the use of this modality (e.g, use of angiotensin converting enzymes [ACE]) will be excluded from participation, until and unless the ACE can be discontinued or replaced with other anti-hypertensives. The TPE protocols and practices for each site will be reviewed by a Co-Investigator (Dr. Pham) with particular expertise, to ensure safety and uniformity.

Rituximab: The patient population will receive pre-treatment with acetaminophen (650mg), diphenhydramine (50mg), and methylpredisolone (100mg IV) prior to drug administration. This regimen will significantly lessen the risk of general reactions to the medication. Patients with contraindications to use of this agent (e.g., past or current hepatitis B or current hepatitis C) will be excluded from participating.

IVIG: Risks of renal injury or anaphylaxis, and other serious side effects (e.g., thrombosis) are obviated by prior hydration, slow IVIG infusions, and excluding patients with IgA deficiency.[79]

Medical treatment for conditions that arise as a result of study participation will not be treated by study personnel. The volunteer will be informed of the problems identified, and this information will be transmitted to the responsible attending physician or physician designated for the subject. In the event of physical injury resulting from the research procedures, medical treatment will be available but not offered free of charge. In addition, financial compensation is not available for wages lost because of injury related to the research protocol. This will be emphasized at the time of consent.

6 STUDY ADMINSTRATION

6.1 REGULATORY AND ETHICAL CONSIDERATIONS

The clinical study will be conducted in accordance with the current IRB-approved clinical protocol; International Conference of Harmonization (ICH) guidelines on Good Clinical Practice, and relevant policies, requirements, and regulations of the IRBs, and applicable federal regulations, including those required under an IND exemption.

The clinical trial will be registered with ClinicalTrials.gov to comply with Section 801 of Public Law 110-85.

The investigators will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled subjects are adequately addressed and that the subjects are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit ratio of study participation, the investigators will obtain the informed consent of enrolled subjects for continued participation in the clinical study.

6.2 PROTOCOL DEVELOPMENT

6.2.1 Activation of a protocol

The Protocol Chair (Dr. Duncan) is responsible for the coordination, development, and approval of the protocol as well as its subsequent amendments, and reporting serious adverse events, violations and deviations per IRB guidelines. .

To meet these requirements, the Protocol Chair will be responsible for the following minimum standards:

- Identify, qualify and initiate participating institutions and obtain accrual commitments.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the Protocol Chair.
- Ensure that there is only one version of the protocol and that all participating institutions use the correct version.
- Oversee the development of data collection forms (case report forms) that are of common format for use at all the participating institutions.

6.2.2 Coordinating Center Support Function

The UAB study team will provide administrative and clerical support to the Protocol Chair for the development and distribution of the protocol.

The tasks to be performed by the UAB study team include:

- Maintain Regulatory documents for all participating institutions.
- Review of the protocol and consent to check for logistics, spelling, and consistency. Provide the Protocol Chair a list of queries related to any inconsistencies.
- Provide necessary administrative sections, including paragraphs related to randomization, data management schedules, and multi-center guidelines.
- Maintenance of contact list of all participating institutions in the multi-center protocol and the distribution of updates to the sites as needed.
- Assistance in preparation and maintenance of case report forms.
- Conduct regular communications with all participating institutions (conference call, emails, etc)
- Maintain documentation of all communications.

6.3 PROTOCOL MANAGEMENT

The CCC is responsible for assuring that each participating institution has the appropriate assurance on file with the Office of Human Research Protection (OHRP). Additionally, the CCC must maintain copies of all IRB approvals, for each participating institution.

6.3.1 Protocol distribution

The CCC will distribute the final approved protocol and any subsequent amended protocols to all participating institutions.

6.3.2 Protocol revisions and closures

The participating institutions will receive phone, fax, mail or e-mail notification of protocol revisions from the CCC or designee. It is the individual participating institution’s responsibility to notify its IRB of these revisions.

Non life-threatening revisions: Participating institutions will receive written notification of protocol revisions regarding non life-threatening events from the CCC or designee. Non-life-threatening protocol revisions should be IRB approved and implemented within 90 days from receipt of the notification.

Revisions for life-threatening causes: Participating institutions will receive telephone notification from the CCC or designee concerning protocol revisions required to protect lives with follow-up by fax, mail or e-mail. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval

Protocol closures and temporary holds: Participating institutions will receive fax, e-mail, or phone notification of protocol closures and temporary holds from the CCC or designee. Closures and holds will be effective immediately. In addition, the CCC or designee will update the participating institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

6.3.4. Protocol deviations and violations: These events are defined here as:

> **Protocol Deviation**: An accidental or unintended study activity that diverges from the IRB-approved protocol, e.g., missing a study window because the subject is traveling, or test that cannot be performed because of scheduling conflicts, etc. Implicit to this definition is the lack of serious consequences that typically does not render a subject ineligible or require their discontinuation from the study.
>
> **Protocol Violation**: A serious non-compliance or protocol divergence that materially reduces the quality or completeness of the data, or makes the ICF inaccurate, or impacts a subject's safety, rights, or welfare. Violations may require exclusion of patients from eligibility analysis or discontinuation from the study. Examples include inadequate informed consent, use of prohibited medication, multiple visits outside permissible windows, etc.

Protocol deviations will continue to be routinely reported to the DCC using eCRF (Form F14). Protocol violations should, in addition, be reported directly to the CCC PI (Dr. Duncan) within 7 working days. Equivocal cases will in turn be presented by the CCC PI to other site PIs for adjudication. Unequivocal or adjudicated protocol violations will be reported by the DCC and/or CCC PI to the DSMB within two weeks. These reporting requirement do not supplant or modify pre-existing requirements for AE reporting (see Section 5.4.7)

6.4 INFORMED CONSENT REQUIREMENTS

The CCC-approved informed consent document will serve as a template for the informed consent from participating institutions. Participating sites are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the CCC for their revision prior to submission to the participating site's IRB.

The Principal Investigator at each participating institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols.

All study participants in this study will be provided a consent form describing the study and providing sufficient information for participants to make informed decisions about their

participation in this study. This consent form will be submitted along with the protocol for review and approval by the IRB at each participating center. The study participant MUST be consented with the IRB approved consent form before the participant is subjected to any study procedures. The approved consent form MUST be signed and dated by the study participant and the investigator obtaining the consent.

6.5 IRB DOCUMENTATION

Sites must obtain local IRB initial approval. The following must be on file with the CCC or designee and must be submitted and approved by the Coordinating Center prior to initiation of the study:

- Approval Letter of the institution's IRB
- Copy of the Informed Consent Form approved by the participating institution's IRB
- IRB approval for all amendments

It is the participating institution's responsibility to notify its IRB of protocol amendments. Participating institutions will have 90 days from receipt to provide the CCC their IRB approval for amendments to a protocol.

6.5.1 IRB Renewal Approval

Annual IRB renewal approval from the participating institution is required in order to continue research and recruit participants onto a protocol. There is no grace period for continuing approvals.

6.6 QUALITY CONTROL AND QUALITY ASSURANCE

To ensure the human subject protection, study procedures, laboratory, study intervention administration, and data collection processes are of high quality and meet GCP and, when appropriate, regulatory guidelines, the DCC may conduct a quality assurance audit (site monitoring) of the site records at any time during or after completion of the study. Audits of a random selection of data, and all protocol consents will also be reviewed.

Monitoring will be scheduled periodically throughout the conduct of the study to assure compliance with the approved protocol, and to verify the completeness and accuracy of study data. Monitoring also aids in identifying any research-related problems for the investigator to correct. A brief written report on each audit or site visit will be prepared by the DCC and sent to the clinical center, DSMB, and NHLBI after each site visit.

6.7 DATA HANDLING AND RECORD-KEEPING

6.7.1 Data recording/Case Report Forms

Case report forms (CRFs) are the primary data collection instruments for the study. All data requested on the CRFs must be recorded, and any missing data must be explained. If a space is left blank because the procedure was not done or the question was not asked, "N/D" must be noted. If the item is not applicable to the individual case "N/A" must be noted. All entries must be printed legibly in black ink on the paper case report forms. In the event of any entry errors, corrections must be made by drawing a single straight line through the incorrect entry, writing the initials of the person making the correction, recording the date when the correction is being made, and entering the correct data above the strike through.

Data elements that are extracted from the medical record (such as participant history or official clinical interpretations of images, pathology, or surgery results) and recorded on the case report forms (CRFs) will be audited against the appropriate component of the medical record. The investigator will review, approve and sign/date each completed CRF; the investigator's signature serving as attestation of the investigator's responsibility for ensuring that all clinical and laboratory data entered on the CRF are complete, accurate and authentic.
Source Data are the clinical findings and observations, laboratory and test data, and other information contained in *Source Documents*. *Source Documents* are the original records (and certified copies of original records); including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, etc. Information recorded on the CRF must be consistent with the *Source Data* recorded on the *Source Documents* or discrepancies must be explained.

Source data are found in all information, original records of findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents represent the first recording of any observations made or data generated about a study participant while he or she is enrolled in a clinical trial. Source documents for each study participant substantiate the data that are submitted to DCC.

Research records for each case should contain copies of the source documents for the data reported to DCC. If data is abstracted from medical charts that are not filed at the investigative sites (e.g. hospital charts), copies of these records should be filed in the research chart. However, every attempt must be made to obtain all records/charts that were used to abstract any study data for this protocol at the time of the audit visit. This will prevent any discrepancies and the inability to verify the document and the data reported.

The CRFs must be kept current to reflect subject status at each phase during the course of the trial. In all cases, subjects must not be identified on the CRF by name. Appropriate coded identifications (i.e. Subject ID number) will be used. Every effort will be made to collect complete data for each study visit. Causes of *missing data* will be fully documented. With respect to safety evaluation, it is not planned to impute missing data.

6.7.1 Record maintenance and retention

Following closure of the study, the investigator must maintain all site study records in a safe and secure location. The records must be easily accessible when needed (e.g., for the DCC audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

The minimum retention time will meet the strictest standard applicable to each participating site, as dictated by local laws/regulations, and/or institutional requirements.

7 COSTS AND PAYMENTS

7.1 COSTS

Salaries and costs of the research physicians and staff conducting this study will be borne by the NIH grant. The cost of the autoantibody reduction therapy, items and services required to provide these treatments, and items or services required to prevent, diagnose, or treat complications of the therapy will be paid by the subject's insurance. This is necessary given the nature of the interventions, size of the trial, and the structure of and resources available from the FOA (PAR-13-128).

The following, from the Centers for Medicare and Medicaid Services website is apropos: (https://www.cms.gov/CCIIO/Resources/FAct-Sheets-and FAQs/aca_ implementation_ faqs15.html), that reads in part:

Coverage for Individuals Participating in Approved Clinical Trials: *In general, PHS Act section 2709(a), as added by the Affordable Care Act, states that if a group health plan or health insurance issuer in the group and individual health insurance market provides coverage to a qualified individual (as defined under PHS Act section 2709(b)), then such plan or issuer: (1) may not deny the qualified individual participation in an approved clinical trial with respect to the treatment of cancer or another life-threatening disease or condition; (2) may not deny (or limit or impose additional conditions on) the coverage of routine patient costs for items and services furnished in connection with participation in the trial [see definition of routine patient costs below]; and (3) may not discriminate against the individual on the basis of the individual's participation in the trial. A qualified individual under PHS Act section 2709(b) is generally a participant or beneficiary who is eligible to participate in an approved clinical trial according to the trial protocol with respect to the treatment of cancer or another life-threatening disease or condition; and either: (1) the referring health care professional is a participating provider and has concluded that the individual's participation in such trial would be appropriate; or (2) the participant or beneficiary provides medical and scientific information establishing that the individual's participation in such trial would be appropriate.*

Moreover, Medicare is expressly mandated to pay for costs of care in clinical trials, and our potential study population is predominantly covered by Medicare. The population of potential subjects in our tertiary referral Centers is so much greater than that needed for this study that we could easily meet enrollment targets if we had to using only Medicare patients (but again, this is not anticipated). The relevant mandate follows:

The Medicare National Coverage Determination (NCD) for Routine Costs in Clinical Trials (310.1) stipulates that Medicare covers the routine costs of qualifying clinical trials, defined as follows: Routine costs include all items and services that "are generally available to Medicare beneficiaries that are provided in the experimental or the control arm of a clinical trial" and that are needed for "the provision of the investigational item or service, the clinically appropriate monitoring of the effects of the item or service, or the prevention of complications" and for "reasonable and necessary care arising from the provision of an investigational item or service in particular, for the diagnosis and treatment of complications." Clinical trials are deemed automatically qualified for this coverage if they are funded by the NIH or selected other government organizations.

The proposed clinical trial meets the three major requirements for Medicare coverage: 1.) The subject or purpose of the trial must be the evaluation of an item or service that falls within a Medicare benefit category (e.g., physicians' service, durable medical equipment, diagnostic test)

and is not statutorily excluded from coverage (e.g., cosmetic surgery, hearing aids); 2.) The trial must not be designed exclusively to test toxicity or disease pathophysiology. It must have therapeutic intent; and 3.) Trials of therapeutic interventions must enroll patients with diagnosed disease rather than healthy volunteers. Trials of diagnostic interventions may enroll healthy patients in order to have a proper control group. Additional relevant information is available on: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=1&ncdver=2&bc=BAABAAAAAAAA

All TAU medications, other routine lab tests, and any other clinical diagnostic or treatment procedures will be considered routine medical care and will be billed to the subjects' health insurance company. Subjects will be responsible for paying any deductibles, co-payments or co-insurance that are a normal part of their health insurance plan. Subjects who do not have health insurance will be responsible for these costs.

Costs for shipping experimental specimens and performing ancillary experimental tests (see Section 2.8.3), such as anti-HEp-2 titers and fluorescent patterns, autoantibody repertoires, serum Ig levels, BLyS concentrations, and others, will be borne by the research grant (UO1HL133232).

7.2 PAYMENTS

Participation in this protocol is completely voluntary. Subjects will not be compensated for their participation in this research study. Travel costs, for subjects returning for serial outpatient assessments, may be provided on an as-needed basis, based on Federal mileage rates and to a maximum per visit of $200. Parking will be provided at no cost while at the research clinic.

8 QUALIFICATIONS AND SOURCES OF SUPPORT

8.1 QUALIFICATIONS OF THE PRINCIPLE INVESTIGATORS

Steven R. Duncan, M.D., Principal Investigator. Professor of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine (PACCM), University of Alabama at Birmingham (UAB). Dr. Duncan is the contact PI of this proposal. He is an attending physician on the pulmonary medicine service at UAB Hospital and clinics, and has been trained in cellular and molecular immunology. Dr. Duncan directs the Program in Immunology of Chronic Lung Diseases at UAB. He will have primary responsibility for protocol development, founding of the coordinating center, fulfillment of administrative, regulatory and legal requirements, development of data acquisition methods in conjunction with the DCC, and interface with the PIs at the collaborating centers, the DSMB and IRB, etc. Dr. Duncan will also participate in direct clinical care of research subjects at UAB. Dr. Duncan will also supervise and direct the end-point immunologic assays, collation of clinical and research findings, data analyses, and manuscript preparation.

Gerard (Jerry) Criner, M.D., Principle Investigator. Professor of Medicine, Temple University. Dr. Criner is an attending physician on the pulmonary medicine services at Temple University hospitals and clinics. He is the Pulmonary and Critical Care Medicine Director, Chairman of the Thoracic Medicine and Surgery Department at Temple, and Director of the Temple Lung Institute. He is the author or co-author of numerous studies of chronic lung

disease, including IPF, and PI or Co-PI of previous and ongoing clinical trials involving patients with IPF and other chronic lung disease.

Daniel J. Kass, M.D., Principal Investigator. Associate Professor of Medicine, Division of Pulmonary, Allergy, and Critical Care Medicine, University of Pittsburgh School of Medicine. Dr. Kass is an attending physician on pulmonary medicine services at the University of Pittsburgh Medical Center (UPMC), and Director of the Dorothy P. and Richard P. Simmons Center for Interstitial Lung Disease at UPMC. Dr. Kass has an active, NIH-funded basic research program in IPF, and considerable expertise in conducting clinical trials in this disease population.

Ivan O. Rosas, M.D., Principle Investigator. Professor of Medicine, Baylor University. Dr. Rosas is the Pulmonary Division Chief, and an attending physician on the pulmonary medicine services at Baylor University Medical Center. He is a highly regarded researcher in the field of interstitial lung disease and IPF, having authored or co-authored dozens of relevant papers, and he is the PI or Co-Investigator of numerous clinical trials.

8.2 SOURCE OF SUPPORT

National Heart, Lung, and Blood Institute (UO1HL133232)

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Modifications as of June 4, 2018

Amendments and Modifications to Earlier Versions of STRIVE-IPF

Protocol Modifications
Note: an asterisk (*) denotes changes recommended or mandated by DSMB

1) The date and version number were updated on header and Synopsis (now v2.2 June 4, 2018).
2) The NCT number, which was assigned during the interval, has been added to the Synopsis.
3) Personnel changes include substitution of Dr. Williams for Dr. Pham, and Dr. Valentine for Dr. Stigler (Synopsis).
4) The number of acute exacerbations of IPF (AE-IPF) has been added as a secondary endpoint (Synopsis and Section 2.8.2).*
5) An independent adjudication process has been added, in which diagnoses prior to randomization are confirmed by another study investigator (Synopsis, Section 2.2 and 2.7.2).*
6) Changes to Inclusion Criteria include specifications that potential participants need to be hospitalized and diagnoses confirmed by site PI (see also modification #5) (Synopsis and Section 3.2).*
7) Requirement that participants have to have ability and willingness to give informed consent and adhere to study requirements (Inclusion criteria #5) supplants formal prohibition of surrogate consent (Synopsis and Section 3.2).*
8) Prior exclusion of any participant who received rituximab at any previous time has been modified to only exclude if this drug was given within the last year (Synopsis and Section 3.2).*
9) Former prohibition that precluded enrollment of any participant with a prior history of malignancy (excepting low grade skin and prostate cancers) was replaced with exclusion limited to those with active malignancy (again, excepting low grade skin and prostate cancer) (Synopsis and Section 3.2).*
10) Slight re-wording, without sustentative changes, to exclusions of those whom the PI believes other considerations preclude safe study or who have contraindications to TPE (Synopsis and Section 3.2).*
11) Addition of anti-neutophil cytoplasmic autoantibody (ANCA) to list of autoimmune tests that preclude randomization (Synopsis and Section 3.2).*
12) Addition of formal requirement that intubation precludes enrollment (this is redundant with modification #7 above, since intubation effectively prevents giving informed consent) (Synopsis and Section 3.2).*
13) Formal addition of clinical and morphological features of idiopathic pneumonitis with autoimmune features to exclusion criteria (Synopsis and Section 3.2).*
14) Altered requirement for prophylactic antibiotic use in those patients who were already treated with same at time of enrollment, so as to prevent over-treatment (Section 2.3).
15) The usual antibiotic course has been added to the Treatment schema (Section 2.5).

16) An aliquot of the collected plasma of the first therapeutic plasma exchange (TPE) from patients who are undergoing repeat treatment for relapses will be collected, stored and used in experimental assays. These plasma specimens are normally discarded (Section 2.6).
17) Aliquots of the therapeutic plasma exchange (TPE), which are otherwise discarded, will also be procured from TPE#3 and #6, in addition to the first and last TPE (#9) that were previously described (Section 2.7).
18) Blood collection has been modified to include 39 ml during the baseline evaluation, an increase of 10 ml, from the previous 29 ml collection. The increase will enable us to perform all protocol-specific qualifying tests (e.g., autoimmune serologies, viral studies, etc.), as well as the experimental immunology tests. The blood draw (of 29 ml) that had been scheduled for day 19 has now been omitted, so total blood procured for this protocol is lessened (Section 2.7).
19) Quality of life (QOL) measures, specifically the K-BILD questionnaire, have been added for 3 month and 6 month assessments (Section 2.8.2).*
20) Added stipulations that TAU cannot cross-over to experimental arm therapies during the observation period, given the analyses here being based on intent-to-treat (Section 2.9.1).*
21) Modified description of primary endpoint analysis (Section 2.9.2)*
22) Changed interim analysis from efficacy analysis to safety (Section 2.9.3)*
23) Changed timelines of reporting adverse events to NHLBI standards: Those that are life-threatening or fatal unexpected adverse events associated with the use of the study drug or procedures will be reported to the contact PI, DCC, NHLBI, DSMB, the local IRB, and central IRB (for the CCC) within seven (7) calendar days of discovery of the incident. Serious (but not fatal or life-threatening) and unexpected adverse events associated with the use of the study drugs or procedures must be reported to the DCC, NHLBI, DSMB, the local IRB, and central IRB (for the CCC) within 15 calendar days. (Section 5.4.7).*

Modifications as of June 4, 2018

Informed Consent Form (ICF) Modifications to Earlier Versions
Note: an asterisk (*) denotes changes recommended or mandated by DSMB

1) The date and version number were updated on footer (now v3.1 June 4, 2018).
2) Personnel changes include substitution of Dr. Williams for Dr. Pham, and Dr. Valentine for Dr. Stigler (face page).
3) Text changes, ostensibly to make this easier to understand, are made throughout this ICF (each page- see tracked changes)*
4) The Explanation of Procedures (starting on page 4) have been summarized with redundancies removed, again at the request of a DSMB member to "make this easier to understand" (starting on Page 5).*
5) Blood collection has been modified to include 39 ml during the baseline evaluation, an increase of 10 ml, from the previous 29 ml collection. The increase will enable us to perform all protocol-specific qualifying tests (e.g., autoimmune serologies, viral studies,

etc.), as well as the experimental immunology tests. The blood draw (of 29 ml) that had been scheduled for day 19 has now been omitted, so total blood procured for this protocol is lessened (Explanation of Procedures- Screening and Baseline).
6) Little boxes that enclose the first description of the particular procedures have been added.*
7) Tables that schematize the tests and procedures have been added (pages 4 and 7).*
8) The blood draw for experimental lab assays on day 19 has been omitted (page 6).
9) Quality of life (QOL) measures, specifically the K-BILD questionnaire, have been added for 3 month and 6 month assessments (page 6).*
10) The possibility of fatal reactions to rituximab has been added. To our knowledge these only occur in lymphoma patients, are probably related to tumor lysis, and do not occur in patients getting the drug to treat antibody-mediated diseases, but this warning is nonetheless added here (page 11).*
11) The study termination criterion of "…if approved by the FDA" was removed (page 15)*

Protocol Modifications: Modifications made that resulted in version 3.1 (dated Jan. 21, 2019)

Note: an asterisk (*) denotes changes recommended or mandated by DSMB

1) The date and version number were updated on header and Synopsis (now becoming v3.1, Jan 21, 2019).

2) Residual and incorrect references to acquiring blood specimens for experimental immunology assays on day 19 have been omitted throughout the protocol (e.g., pages 15 and 23).

3) A series of further clarifications to the protocol regarding treatments of AE-IPF relapses* These are located now on pages 18 and 25. They include:

a) a more detailed definition of what constitutes an AE-IPF relapse

b) omission of the former stipulation that required hospital discharge, after interval improvement with therapy, in order to be eligible for rescue re-treatment.

c) a stipulation that 5 days need to elapse between completion of the initial treatment and the AE-IPF relapse, in order to re-implement rescue therapy.

d) addition of a consensus adjudication process among the majority of PIs to substantiate the diagnoses of AE-IPF relapses, prior to rescue re-treatment.

4) Various typo's and mis-spelled words have been corrected throughout this document

5) The TPE collection schedule has been added to Table 1

Informed Consent Form (ICF) Modifications (becoming V4. Jan 21. 2019)

Note: an asterisk (*) denotes changes recommended or mandated by DSMB

1) The date and version number were updated on the ICF face page footer.

2) The ICF now clearly states participants randomized to the experimental treatment arm will be eligible for one re-treatment with an AE-IPF relapse that occurs during their 6-month participation in the trial. A second relapse occurring in this subpopulation, or relapses occurring in TAU arm participants, will be treated with the TAU protocol.*

3) The protocol for experimental treatment of AE-IPF relapses has been clarified to describe five TPE at every other day intervals, followed by the IVIG.*

4) The supplemental ICF to allow genetic testing has been modified to mention some possible uses.*

Protocol Modifications to v. 3.1 (Jan 21, 2019) that resulted in Version 4.0 (dated August 18, 2019)

1) The potential for thrombotic complications of IVIG is now described on pages 38 and 45

2) ANCA has been removed as an exclusion criterion (pages 8, 20, 35)

3) Hepatitis C antibody (HCV Ab) tests will continue to be used in screening, but positive results will lead to testing by HCV nucleic acid PCR tests. Patients who are merely HCV Ab+ but have negative PCR assays will be eligible for further consideration and possible randomization (pages 7,20,35)

4) Ionized calcium measures are no longer an absolute requirement prior to TPE, but can continue to be obtained at the discretion of attending physicians (pages 20-22)

5) A section has been added to the protocol (Section 6.3.4) to define, distinguish, and standardize Protocol Violations and Protocol Deviations, as well as detail reporting requirements for the former (pages 47 and 48)

6) We've added two items to the Table of Contents, to make it easier to locate appropriate Protocol sections and page numbers for AE reporting timelines, and Protocol violation and deviation definitions.

7) Interval personnel changes are noted. Dr. Cutter's position as DCC head has been assumed by Dr. Fazlur. Dr. De Andrade has relocated and is no longer a STRIVE Co-Invest.

Protocol Modifications to v. 4.0 (August 18, 2019) that resulted in Version 5.0 (dated September 3, 2019).

The ICF Modification describing potential thrombotic and bleeding AE with IVIG was corrected.

Informed Consent Form (ICF) Modifications to V4.0 dated Jan 21, 2019 (becoming V5. August 18. 2019)

1) The potential for thrombotic complications of IVIG is now described on page 12

2) The potential maximal number of subject recruitments at UAB during the duration of this trial has been increased to 24.

Informed Consent Form (ICF) Modifications to V5.0 dated August 18, 2019 (becoming V5.1. September 3. 2019)

Six words missing from the description of potential bleeding and clotting AE with IVIG, originally approved, have been re-added (page 12)

Protocol Modifications to V.5.0 dated September 3, 2019, that resulted in Version 6.0 (dated May 7, 2020)

1) Dates and version numbers have been updated throughout

2) The participating sites currently active have been updated

3) The current Co-Investigator list has been updated

4) A typo has been corrected to clarify collection of plasma discards during AE-IPF relapses (pg 21)