AMENDED STUDY PROTOCOL

Extracorporeal Photopheresis for the Management of Progressive Bronchiolitis Obliterans Syndrome in Medicare-Eligible Recipients of Lung Allografts (CAG-00324R2)

Date of submission:	July 29, 2017
Protocol Version:	Version 7.0
Principal Investigator:	George J. Despotis, MD[1] Associate Professor of Pathology, Immunology & Anesthesiology Department of Pathology and Immunology Washington University St. Louis School of Medicine 660 South Euclid Avenue, Campus Box 8118 St. Louis, MO 63110 (314) 362-6586 (314) 747-3977 fax gjdespotis@wustl.edu
Lead Academic Investigator	Ramsey R. Hachem, MD[1] Professor of Medicine, Pulmonary & Critical Care Medicine Washington University St. Louis School of Medicine 660 South Euclid Avenue, Campus Box 8052 St. Louis, MO 63110 (314) 454-8766 (314) 454-5571 fax rhachem@dom.wustl.edu
Biostatistician:	Edward Spitznagel, PhD[1] Professor of Mathematics; Joint Appointment in Biostatistics Department of Mathematics Washington University in St. Louis One Brookings Drive, Campus Box 1146 St. Louis, MO 63130
ARO Co-Director Director, Clinical Coordinating Center	Suresh Vedantham, MD[1] Professor of Radiology & Surgery Washington University St. Louis School of Medicine Mallinckrodt Institute of Radiology 510 South Kingshighway Blvd. St. Louis, MO 63110 (314) 362-2923 (314) 747 1944 fax vedanthams@wustl.edu

[1]CVs for Drs. Despotis, Hachem, ~~and~~ Spitznagel, Vedantham, Marcus and Paul Commean are available upon request.

ARO Co-Director
Director, Data Coordinating Center

Daniel S. Marcus, PhD. [1]
Associate Professor of Radiology
Department of Radiology
Washington University St. Louis School of Medicine
4525 Scott Ave, Suite 3339
St. Louis, MO 63110
(314) 362-4562
(314) 747 1944 fax
dmarcus@wustl.edu

Supervisor

Paul Commean, BEE [1]
Assistant Professor of Radiology

Data Coordinating Center

Department of Radiology
Washington University St. Louis School of Medicine
4525 Scott Ave, Office 3361
St. Louis, MO 63110
(314) 362-8497
commeanp@wustl.edu

Study sponsor: Washington University School of Medicine[2]

1.0 BACKGROUND

Lung transplantation has become the treatment of choice for selected patients with end-stage lung disease. However, long-term survival after transplantation remains disappointing - the median survival according to the International Society for Heart and Lung Transplantation (ISHLT) Registry is approximately 5 years. Chronic rejection (bronchiolitis obliterans syndrome [BOS]) has emerged as the leading obstacle to better long-term outcomes and the leading cause of death beyond the first year after transplantation. The histologic hallmark of chronic rejection after lung transplantation is obliterative bronchiolitis (OB). This disorder is a fibroproliferative scarring process that involves the respiratory and membranous bronchioles, resulting in narrowing of the airway lumen and ultimately complete luminal obliteration. Physiologically and clinically, this luminal narrowing results in airflow limitation and breathlessness. Histologic confirmation of OB is difficult with bronchoscopically obtained

[2] Project will be supported with an unrestricted grant from Therakos.

lung biopsies because of the patchy distribution of the disorder and inadequate sampling of small airways with transbronchial lung biopsies. As a result, BOS is diagnosed and staged specifically in accordance with spirometry-measured changes in forced expiratory volume in one second (FEV_1), the clinical surrogate for obliterative bronchiolitis (Table 1):

Table 1. ISHLT definition of bronchiolitis obliterans syndrome (BOS) and its stages

Stage	*Definition*
BOS stage 0	FEV_1 > 90% & $FEF_{25-75\%}$ > 75% of baseline*
BOS stage 0-p	FEV_1 = 81% to 90% of baseline and/or $FEF_{25-75\%}$ ≤ 75% of baseline
BOS stage 1	FEV_1 = 66% to 80% of baseline
BOS stage 2	FEV_1 = 51% to 65% of baseline
BOS stage 3	FEV_1 ≤ 50% of baseline

*Baseline FEV1 is defined as the average of the two highest FEV_1 measurements obtained at least 3 weeks apart after transplantation.

As with COPD and other chronic obstructive pulmonary disease disorders, this progressive physiological impairment of lung function strongly correlates with survival in post-lung transplant patients with progressive BOS. In a large consecutive series of patients (n = 389) receiving a lung transplant between 1992 and 2004, both progression from BOS grade 1 to 2 and from BOS grade 2 to 3 were associated with a three-fold increase in mortality, with hazard ratios of 3.1 (95% CI, 1.2 to 7.9) and 2.9 (95% CI, 1.6 to 5.3), respectively.[3] Investigators at Duke University Medical Center separately characterized the relationship between FEV_1 and mortality in a consecutive series of 51 post-lung transplant patients. In 51 lung allograft recipients admitted to the medical ICU over a two-year period, the ratio of last FEV_1 to best post-transplant FEV_1 was independently associated with hospital survival. Patients who died

[3] Burton CM, Carlsen J, Mortensen J, et al. Long-term survival after lung transplantation depends on development and severity of bronchiolitis obliterans syndrome. *J Heart Lung Transplant* 2007 Jul:26(7):681-6.

had a lower ratio of last FEV_1 to post-transplant best FEV_1 (FEV_1, 51.3 ± 21.9%, n = 14) compared to survivors (FEV_1 75.5 ± 20.4%, n = 30).[4]

In a recent examination of our own previously reported case series of 60 patients with progressive BOS who were treated with extracorporeal photopheresis (ECP),[5] we have independently established a strong association between FEV_1 and mortality. We compared baseline FEV_1 between survivors and non-survivors using non-parametric testing with two-sample Wilcoxon Rank-Sum testing due to unequal variances We found a highly significant difference in baseline FEV_1 between survivors and non-survivors at both 12 and 16 months following initiation of ECP therapy as summarized in Table 2 below:

Table 2. Baseline FEV_1 in survivors and non-survivors 12 and 16 months following initiation of extracorporeal photopheresis (ECP)

Months after initiation of ECP	*Baseline FEV_1 of survivors**	*Baseline FEV_1 of non-survivors**	*p-value*
12	1.57 ± 0.70 L	1.16 ± 0.47 L	0.013
16	1.69 ± 0.75 L	1.16 ± 0.72 L	0.002

*At 12 and 16 months, there were 39 and 30 survivors, respectively.

We additionally examined one-year survival in patients with an FEV_1 below the median baseline FEV_1 value (1.24 liters). Applying logistic regression analysis, patients with a baseline FEV_1 of less than 1.24 liters had an odds ratio of 5.7 for risk of mortality at 12 months following initiation of ECP, in relation to patients with a baseline FEV_1 greater than 1.24 liters.[6]

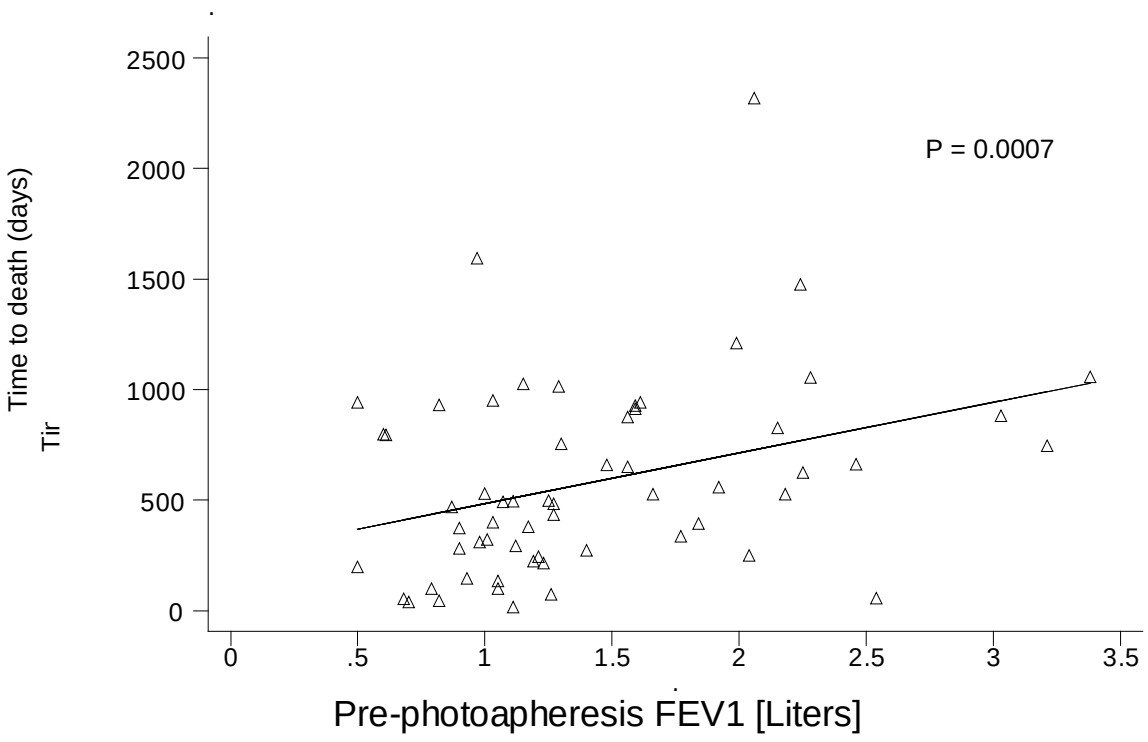
[4] Hadjiliadis D, Steele MP, Govert JA, et al. Outcome of lung transplant patients admitted to the medical ICU. *Chest* 2004;125:1040-5.

[5] Morrell MR, Despotis GJ, Lublin DM, et al. The efficacy of photopheresis for bronchiolitis obliterans syndrome after lung transplantation. *J Heart Lung Transplant* 2010 Apr;29(4):424-31.

[6] Data and analysis on file (G.Despotis, E. Spitznagel, Washington University School of Medicine)

Applying univariate linear regression analysis, we observed a significant relationship between baseline FEV_1 (in liters) and time to death in our 60-patient treatment cohort. This relationship between survival and FEV_1 is graphically represented in Figure 1:

Figure 1. Relationship between baseline FEV_1 and time to death for our 60 patient treatment cohort (based on 12-month mortality findings)



The management of BOS has been disappointing. The cornerstone of treatment has been intensifying the immunosuppressive regimen. The specific approach is variable from center to center, but typically includes optimizing the maintenance immunosuppressive regimen to include tacrolimus and mycophenolate mofetil, high-dose steroids, and a course of anti-thymocyte globulin. Also, maintenance treatment with the macrolide antibiotic, azithromycin, can stabilize lung function in some cases. Nevertheless, the majority of patients does not respond to these interventions and has a progressive decline in lung function resulting in worsening functional status and quality of life and ultimately graft failure and death.

Extracorporeal photopheresis (ECP) has been used at some centers as a salvage treatment for progressive BOS with favorable clinical results in many cases. ECP involves separating the patient's blood into a leukocyte-enriched component (buffy coat) and a leukocyte-depleted component. The buffy coat is then photosensitized with 8-methoxypsoralen and treated with ultraviolet light within a photosensitization chamber, resulting in leukocyte apoptosis. Although the exact mechanism of action of ECP is unclear, reinfusion of this apoptotic leukocyte population into the patient's circulation is thought to result in alterations in antigen presenting cells, cytokine profiles, and the expansion of regulatory T cells. The immunomodulatory effect of ECP has been clearly shown to ameliorate cardiac allograft rejection; ECP is covered for treatment of heart transplant rejection in Medicare beneficiaries.

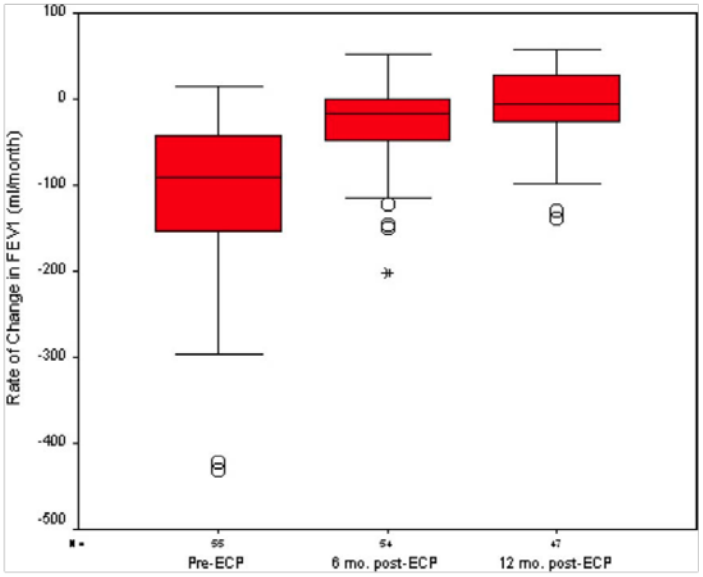
Multiple small case series have described a reduction or stabilization in the rate of decline in lung function after the initiation of ECP for progressive BOS.[7] In the largest case series, Morrell and colleagues reported the results of 60 lung transplant recipients treated with ECP for progressive BOS between 2000 and 2007.[8] Before the initiation of ECP, the mean rate of decline in FEV_1 was -116.0 ml/month. Patients received 24 ECP treatments over 6 months, and the slope of decline in FEV_1 decreased to -28.9 ml/month during the 6-months treatment period; the mean difference in the rate of decline in FEV_1 before the initiation of ECP compared to after ECP was 87.1 ml/month (Figure 1; $p < 0.0001$). Further, 14 patients (25% of the overall group) experienced an improvement in lung function during the 6-month treatment period, by a mean of 120.6 ml compared to the pre-treatment rate of FEV_1 decline. In addition, the change in the rate of decline in FEV_1 for the entire cohort persisted over the ensuing

[7] Reviewed in: Centers for Medicare and Medicaid Services. Final Decision Memorandum for Extracorporeal Photopheresis (CAG-00324R), April 30, 2012.

[8] Morrell MR, Despotis GJ, Lublin DM, et al. The efficacy of photopheresis for bronchiolitis obliterans syndrome after lung transplantation. *J Heart Lung Transplant* 2010 Apr;29(4):424-31.

6 months after completion of the course of ECP; the mean rate of decline in FEV_1 over the 12 months after the initiation of ECP remained at -21.4 ml/month. The mean difference in the rate of decline over the 12-month post-ECP treatment period the 6-month period before ECP initiation was 94.6 ml/month (Figure 2; $p < 0.0001$).

Figure 2. Mean monthly rate of decline in FEV_1, pre-ECP and 6 and 12 months post-ECP



Ten of the 60 patients developed complications during treatment. Eight patients developed catheter-related blood stream infections, one patient developed transient hypotension requiring intravenous fluids during ECP, and one patient developed catheter-related partial thrombosis of the superior vena cava.

In a subgroup of 25 Medicare beneficiaries, the mean rate of decline in FEV_1 during the 6-month period before the initiation of ECP in the Medicare subgroup was -98.7 mL/month. The mean decrement in FEV_1 during this 6-month period was 594 mL. During the 6-month period after the initiation of ECP, the mean rate of decline decreased to -31.9 mL/month; see

Table 3 below. The mean decrement in FEV_1 during the 6 months after ECP initiation was 192 mL. The mean difference in the rate of decline of FEV_1 was 66.8 mL/month (95% confidence interval [CI], 22.0 – 111.4 mL/month; $p < 0.005$).

Table 3. Mean monthly rates of decline in FEV_1, pre-ECP and 6 months post-ECP

Group	6 months prior to ECP (mL)	6 months post-ECP (mL)	*p*-value	Mean difference (mL) (95% CI)
Medicare (n=25)	- 98.7	- 31.9	<0.005	66.8 (22.2 - 111.4)
Non-Medicare (n=31)	- 129.9	- 26.4	<0.0001	103.4 (62.1 - 144.8)
All Patients (n=56)	-116.0	- 28.9	<0.0001	87.1 (57.3 - 116.9)

The analysis was extended to 12 month after the initiation of ECP to evaluate the durability of the response; these findings are presented in **Table 4** below. In the Medicare sub-cohort, the mean rate of decline over the 12 months following initiation of ECP was -24.3 mL/month, and the mean decrement in FEV_1 during this 12-month period was 144 mL. The mean difference in the rate of decline between this 12-month period and the period before ECP was 74.4 mL (95% CI, 30.9 – 117.9 mL/month; $p = 0.002$).

Table 4. Mean monthly rates of decline in FEV_1, pre-ECP and 12 months post-ECP

Group	6 months prior to ECP (mL)	12 months post-ECP (mL)	*p*-value	Mean difference (mL) (95% CI)
Medicare (n=25)	- 98.7	-24.3	0.002	74.4 (30.9 - 117.9)
Non-Medicare (n=31)	- 129.9	-19.1	<0.0001	110.8 (73.0 - 148.7)
All Patients (n=56)	-116.0	-21.4	<0.0001	94.6 (66.5 - 122.6)

The results of this case series and other published reports provide compelling evidence that ECP is a potentially effective treatment for the management of progressive BOS after lung transplantation.

GENERAL CONSIDERATIONS RELATING TO CMS FINAL DECISION MEMO: EXTRACORPOREAL PHOTOPHERESIS (CAG-00324R)

On May 2, 2012, CMS issued a Decision Memo stating that ECP is covered for Medicare beneficiaries for the treatment of BOS following lung allograft transplantation only when the procedure is provided under a clinical research study that addresses one or more aspects of the following question:

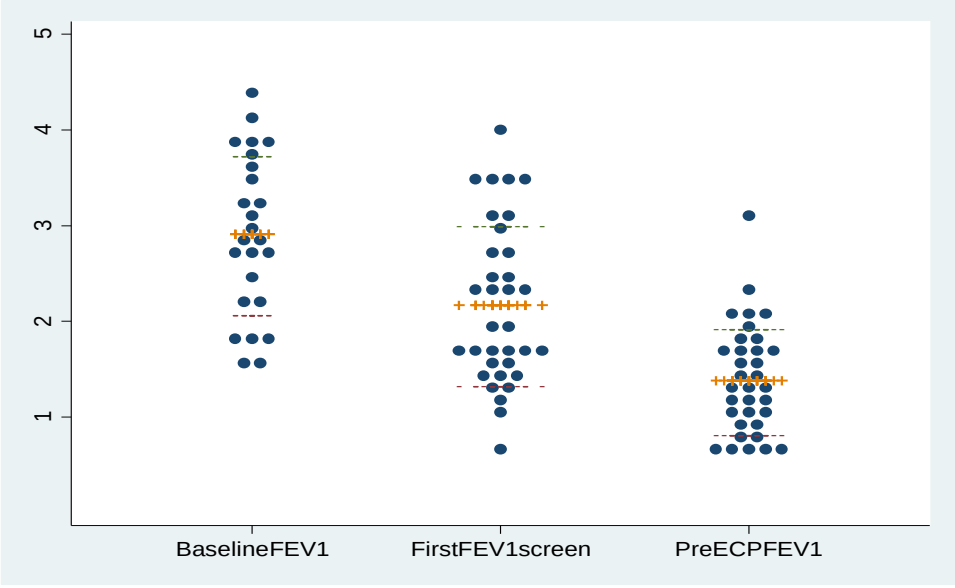
> *Prospectively, do Medicare beneficiaries who have received lung allografts, developed BOS refractory to standard immunosuppressive therapy, and received ECP, experience improved patient-centered health outcomes as indicated by: (a) improved FEV_1, or decreased rate of decline of FEV_1; (b) improved survival after transplant; and/or (c) improved quality of life?*

In light of the compelling evidence that ECP is efficacious and because it has been utilized as a salvage therapy – i.e. it is ordered when standard immunosuppressive drug therapy has failed to adequately slow progression of FEV_1 decline – it is highly unlikely that providers that cur-

rently order ECP for their BOS patients who have already failed optimized immunosuppressive drug therapy would have been willing to randomize half of their patients to continue on their failed drug therapy.

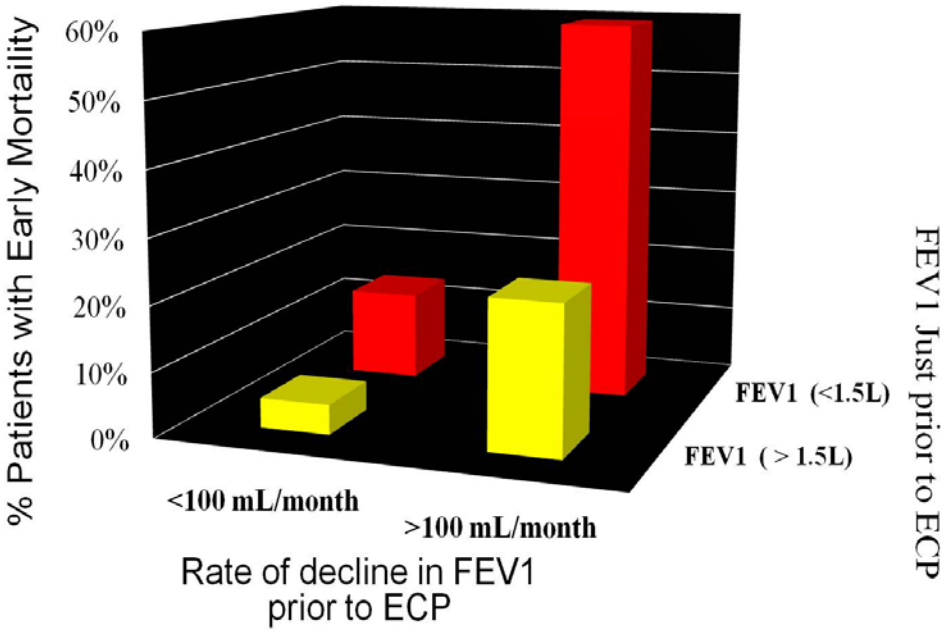
Our recent interim analysis of preliminary data involving 44 enrolled patients in this approved CMS study[9] revealed a higher-than-expected level of early mortality (i.e., 32% mortality prior to completion of the six month ECP regimen) despite stabilization of the rate of FEV-1 decline with ECP therapy. This led us to investigate factors associated with early mortality which identified the following:

1. Etiology of early mortality prior to completion of ECP was designated as "respiratory" or "graft failure" in 91% of patients
2. In the 44 enrolled patients, when compared to baseline post-transplant values, substantial reductions in FEV1 (i.e., a 30% decline from baseline) were observed at the first spirometry screening FEV1 (i.e., 4-6 months prior to ECP) and just prior to initiation of ECP (i.e., a 50% decline from baseline), see figure below:



[9] CMS Protocol Number CAG-00324R2 (Version 4); Clinical Trials.gov identifier: NCT02181257

3. In an analysis involving 33 of 44 enrolled patients, a statistically (p=0.05) greater rate of decline in FEV1 was observed in patients who had early mortality (-254 mL ± 208 mL/month) when compared to those who completed the six month ECP course (-142 mL ± 124 mL/month).
4. Using data from patients who had early mortality from both the current study[10] and our previous publication[11] the early mortality rate was highest (60%) in subjects with pre-ECP FEV1 values < 1.5 Liters and a rate of decline in FEV1 > 100 mL/month (Figure below).

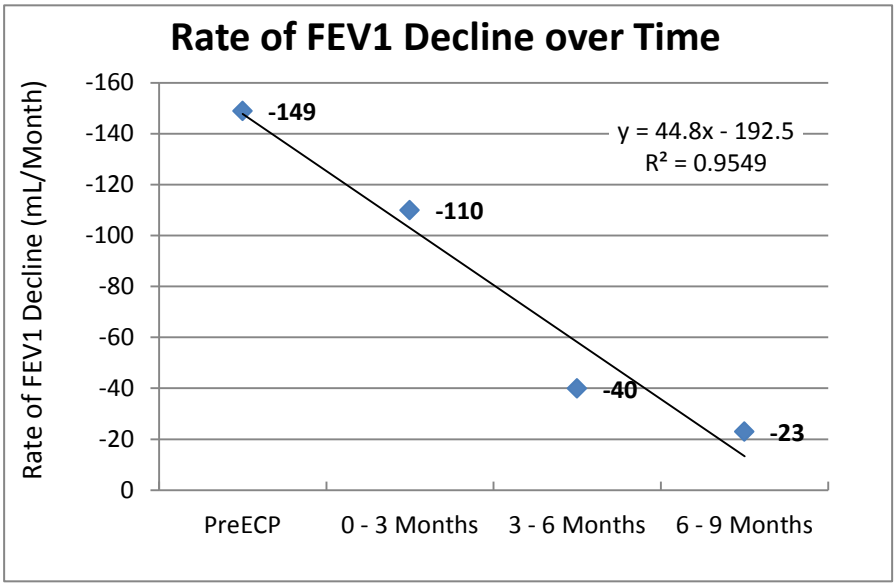


5. In addition, an FEV1 value prior to ECP of < 1.25 L had a 90% sensitivity (i.e., 9/10 patients who died had an FEV1 < 1.25 L) for early mortality in our previous analysis.[11]

[10] CMS Protocol Number CAG-00324R2 (Version 4); Clinical Trials.gov identifier: NCT02181257

[11] Morrell MR, Despotis GJ, Lublin DM, et al. The efficacy of photopheresis for bronchiolitis obliterans syndrome after lung transplantation. *J Heart Lung Transplant* 2010 Apr;29(4):424-31.

Using a subset of patients (n=9) enrolled in the current CMS sponsored study[10] who had FEV1 data available through nine months, we also investigated the accuracy of our current efficacy endpoint (i.e., change in the rate of decline between the pre-intervention period and six months after initiation of ECP) by assessing the mean rate of decline in FEV1 over the following 3 month time periods: Months 0-3, months 3-6 and months 6-9. These findings highlight that the previously designated six month period may not accurately reflect the efficacy of ECP that requires at least six months to fully implement. This conclusion is illustrated by the figure below which demonstrates that the rate of FEV1 decline decreases linearly up to the last measurement period (months 6-9). Of note, the mean rate of decline for months 0-6 was -72 mL/month which would have underestimated the efficacy of the intervention.



Previous publications that have characterized the natural history of BOS have demonstrated that BOS is typically progressive with the vast majority of patients (i.e., 61-81% of tients)[12,13] who continue to have decline in lung function (i.e., develop treatment-refractory

[12] Heng D Sharples LD, McNeil K et al Bronchiolitis Obliterans Syndrome: Incidence, Natural History, Prognosis and Risk Factors. J Heart and Lung Transplantation 1998;17:1255-63

progressive BOS); the estimate of 61% from the more recent study[13] may be underestimated since long term follow-up was not pursued in this study. These studies also demonstrated the majority (i.e., 72-85%) of patients either present or progress to advanced stages of BOS which leads to a 3 year mortality rate of 51-54%.[12,13] Our proposal to revise our protocol to incorporate both early detection and proactive management of BOS with ECP is supported by both our DSMB as well as our local PIs.

Therefore, we propose a protocol revision that would involve two important changes:
1. Early detection of BOS or refractory BOS using a standardized, more frequent spirometry monitoring approach (i.e., defined as using either more frequent laboratory based spirometry every 4-8 weeks or using A Standardized Home Spirometry Monitoring Method pending development and approval[14]) and

2. Early implementation of the intervention (ECP) in both patients with early stage refractory BOS and also as first line therapy in a subset of patients at the initial diagnosis of BOS, in the context of a new randomized controlled trial.

What is not well understood at this time, however, is whether certain coexisting disease states or patient-related demographic, functional, treatment-related or diagnostic variables (e.g. extent or statistical significance of the rate of pre-ECP FEV_1 decline) might prove to have predictive value in identifying subsets of BOS patients that are likely, or unlikely, to experience reduced rate of decline or stabilization in FEV_1 following ECP treatment. Therefore we originally proposed a Registry study to enroll a large series of patients from multiple U.S. centers to (1) confirm that ECP significantly reduces the rate of FEV_1 decline in BOS patients re-

[13] Finland Copeland CA, Snyder LD, Zaas DW et al. Survival after Bronchiolitis Obliterans Syndrome among Bilateral Lung Transplant Recipients. Am J Respir Crit Care Med 2010;182:784-89.
[14] A Standardized Home Spirometry Method will be submitted for approval by our IRB

fractory to standard immunosuppressive drug therapy, and (2) capture and assess specified patient demographic, treatment-related, diagnostic, functional and co-morbidity-related variables that may predict outcomes after ECP therapy. With the current proposed protocol revision, the study will be modified to add a randomized controlled trial (RCT) that will compare outcomes in patients with initial diagnosis of BOS who receive either conventional therapy (i.e., that involves the standard of care at the respective enrolling center) or ECP for first line management of BOS.

2.0 STUDY OBJECTIVES AND DESIGN

The primary aims of this revised study are to determine the efficacy and tolerability of ECP for the treatment of either refractory (i.e., in an expanded series of patients within the original prospective cohort Registry, n=240) or new (i.e., in a new prospective randomized controlled trial sub-study, n=739) BOS after lung transplantation in a large patient series (total patients to be enrolled = 979). In compliance with the Centers for Medicare and Medicaid Services' (CMS) Coverage with Evidence Development (CED) decision, the study will collect specified demographic, comorbidity, treatment, and outcome data exclusively for Medicare beneficiaries who are treated with ECP for either refractory or new BOS. This revised study will include no more than twenty (20) participating centers. Patients will be enrolled from CMS-approved lung transplant centers and other ECP therapy providers with appropriate expertise that agree in writing to comply with the protocol, secure Institutional Review Board (IRB) approval and complete the case report forms. The randomized controlled trial (RCT) component of the revised study that includes patients with an initial diagnosis of BOS, and will enable evaluation of potential survival and quality of life benefits of early treatment of BOS with first-line ECP.

This revised study protocol will be registered on ClinicalTrials.gov following approval by CMS. The original waiver from IND requirements that has been granted for this study by the U.S. Food and Drug Administration (Appendix 1) has been extended to the revised protocol (Appendix 2). Study findings will be disseminated through publication in an appropriate peer-reviewed medical journal (s) and through presentations at academic meetings.

3.0 PATIENT ELIGIBILITY AND ENROLLMENT

3.1 Subject Identification

At the participating clinical centers, potential subjects will be identified by physician investigators and co-investigators, other physicians, and study staff, and through review of relevant administrative databases that are maintained for routine clinical care purposes (e.g. lung transplantation division database, pulmonary function laboratory database, etc.), subject to local IRB approval. Patients may also be referred from external facilities.

3.2 Inclusion criteria (patients must meet <u>all</u> of these criteria):

3.2.1 Inclusion Criteria for Refractory BOS (rBOS) Single-Arm Registry

1. Age (18 years old or older).
2. Medicare-eligible (i.e., patients with both Part A and Part B) status
3. Lung transplant recipient (combined organ transplant recipients, e.g. heart-lung or liver-lung recipients, are eligible).
4. Patients with a diagnosis of BOS using at least two laboratory based FEV1 values obtained at least three weeks apart that are both at least 20% lower than baseline FEV1 using the ISHLT definition (The average of the two highest FEV1 measurements obtained at least 3 weeks apart after transplantation).
5. Refractory BOS defined as ongoing decline in FEV_1 despite at least one of the following treatments: azithromycin, high-dose steroid, anti-thymocyte globulin, total lymphoid irradiation, sirolimus, or everolimus).

6. At minimum five recorded FEV_1 measurements obtained at intervals of at least two weeks apart, over the 6 months preceding study enrollment, of which one FEV_1 must be within two weeks prior to enrollment.
7. History of frequent spirometry monitoring defined as having had regular FEV_1 measurements during the preceding four months prior to enrollment with no time interval between FEV1 measurements that exceeds 8 weeks.
8. A documented clinical assessment including a physical assessment and CBC with WBC within two weeks prior to enrollment.

3.2.2 Inclusion Criteria for Newly Diagnosed BOS Randomized Controlled Trial (patients must meet <u>all</u> of these criteria)

1. Age (18 years old or older)
2. Medicare-eligible status (i.e., patients with both Part A and Part B)
3. Lung transplant recipient (combined organ transplant recipients, e.g. heart-lung or liver-lung recipients, are eligible).
4. History of close FEV1 monitoring prior to diagnosis of new BOS defined as having had either of the two monitoring approaches:

   <u>Frequent laboratory based spirometry</u> defined as having had regular FEV1 measurements during the preceding six months prior to diagnosis of new BOS with no time interval between FEV1 measurements that exceeds 8 weeks.

   <u>Frequent Home Spirometry</u> through a Standardized Home Spirometry Method: this Method is currently being finalized and will not be utilized to meet this close monitoring enrollment criteria until it is IRB approved.

5. Diagnosis of new BOS (i.e., "new BOS" is defined as within six weeks of enrollment) based on laboratory-based spirometric FEV1 measurements obtained on at least two separate occasions (i.e., at least 3 weeks apart) that have declined by more than 20% from post-transplant baseline values (i.e., using ISHLT definition). Inherent to the di-

agnosis of new BOS is the exclusion of other potential causes of allograft dysfunction such as acute rejection, respiratory tract infection, and airway anastomotic complications. Thus, sites are encouraged to conduct appropriate evaluation for declining allograft function including bronchoscopy with BAL and lung biopsies if clinically appropriate to exclude other potential causes of allograft dysfunction.

6. Achievement of a statistically significant rate of decline in lung function (FEV1) at the diagnosis of new BOS per the criteria in Section 3.6 as assessed by the following criteria:

   For patients who are monitored with laboratory based spirometry, at least five recorded FEV_1 measurements obtained at intervals of at least two weeks apart, over the 6 months preceding study enrollment accompanied by a statistically significant ($p<0.05$) rate of decline of FEV1 that exceeds 30 mL/month; or

   For patients who are monitored with home Spirometry (subject to IRB approval), the Standardized Home Spirometry Method will define the specific criteria that will be used for these patients.

7. Documented clinical assessment including a physical assessment and a CBC with WBC within two weeks prior to enrollment.

3.3 Exclusion criteria (subjects meeting any one of these criteria will be excluded):

1. Current participation in another clinical treatment trial with an investigational agent.
2. Any condition that may interfere with the subject's ability to perform pulmonary function testing.
3. Known allergy or hypersensitivity to pharmacologic agents used during ECP
4. Any condition that would significantly affect the participant's ability to adhere to the protocol, affect interpretation of the study results, or put the participant at unacceptable risk for study-related complications as judged by the referring clinician. This

may include a) patients with a specific acute contraindication to receiving ECP due to any acute condition such as new or evolving myocardial infarction or central nervous system disorder, hemodynamic instability or hypovolemia, acute bleeding, respiratory distress; or b) patients with lupus erythematosus, porphyria cutanea tarda, erythropoietic protoporphyria, variegate porphyria, xeroderma pigmentosum, albinism, or other dermatologic or ocular condition that contraindicates the use of methoxsalen or markedly enhances photosensitivity in the investigator's judgment.

5. Aphakia or absence of ocular lenses
6. Pregnancy (positive pregnancy test - a urine or blood pregnancy test must be obtained within ~~2~~1 weeks prior to enrollment in women of childbearing potential)
7. Inability to provide informed consent or to comply with study treatments or assessments (e.g. due to cognitive impairment or geographic distance)
8. Recent (i.e., within 2 weeks prior to enrollment) leukopenia (white blood cell count < 3,000 cells/mm^3)
9. Patients whose decline in lung function (FEV1) is related to either Restrictive CLAD or other causes that do not represent BOS such as pneumonia, heart failure, etc.

For patients under review for eligibility for ECP for refractory BOS:

10. The most recent FEV1 $\leq$ 900 mL
11. Rate of FEV1 decline within the last 6 months $\geq$ 300 mL/month.

For patients under review for eligibility for RCT:

12. any patient who at least one year after transplant is treated with either lymphocyte depleting therapy or with an escalated dose of steroids (i.e., prednisone greater than 30 mg/day) for more than one month for an acute decline in lung function that is suspected to be secondary to acute cellular rejection.

3.4 Compliance with Federal Guidelines Pertaining to Study Eligibility

All participating study sites will be required to include, in their written protocols submitted to their Institutional Review Boards (IRBs) for approval, a clause stating that patient eligibility for enrollment will not be influenced in any way by gender, racial or ethnic status. As a condition of participation, sites will be required to affirm in writing that their participation in this research study will be conducted in compliance with all applicable federal regulations concerning the protection of human subjects found in 45 CFR Part 46.

3.5 Screening Procedures and Informed Consent

When a potential subject is identified, the investigator and/or an appropriately designated staff member will screen the medical history, laboratory studies, and past pulmonary function tests to confirm that the patient may be eligible. When a potentially eligible patient is identified, a member of the research team will contact the patient's physician to obtain permission to enroll the patient. If the patient's physician or a research team member believes that the patient is cognitively impaired or otherwise unable to provide informed consent, or if there is suspicion that the recent decline in lung function is due to an acute infection, the patient should not be invited to participate in the study. All subjects should be able to understand the nature of the research and their participation, show the ability to consider alternatives including the option of non-participation, and show the ability to make a reasoned choice. All subjects will be informed that they are being asked for permission to allow the study team to collect their medical information irrespective of whether they are treated with ECP in the study.

Subjects with Refractory BOS who agree to participate in the Registry study will be informed of the following: to limit the use (and attendant risks) of ECP therapy to those patients who are most likely to benefit, their eligibility to receive ECP within the study will be

determined by the study team's analysis of their pre-enrollment pulmonary function testing along with input from their physician.

Subjects with Newly-Diagnosed BOS who agree to participate in the study will be informed that they will be randomly assigned to either a control group (Control) who will receive the local Standard of Care for management of their BOS or to an Early Photopheresis Intervention (EPI) group who will receive ECP as first line management of BOS. (See lower flow diagram in Appendix 3).

The investigator or a designee should explain the study to the patient in a non-coercive manner and provide him/her with a Study Informed Consent Form to review, sign, and date. A copy should be provided to the patient and the original retained by the study team. For subjects who are not fluent in English, the informed consent process should be conducted in the subject's native language, utilizing a qualified translator when appropriate. All patients must provide written informed consent prior to enrollment per the local IRB's policy. After written informed consent is obtained and assuming the patient meets all eligibility criteria, the investigator or a designee should enter the patient's information on the web-based eligibility form to formally request that the patient be enrolled. A physical examination, vital signs, and pulmonary function testing should be documented within 2 weeks prior to enrollment. In women of child-bearing potential, a negative urine or blood pregnancy test should be documented within two weeks prior to enrollment.

Patients for whom study eligibility and written informed consent are confirmed online by the site research team will be assigned a unique participant identification Number by the online registration system, at which time they will be considered enrolled in the study.

3.6 Treatment Allocation

3.6.1 Patients with Refractory BOS (Registry Study)

All patients with refractory BOS will be electronically assigned to either a **ECP Treatment cohort** or to an **Observation cohort** based upon the FEV_1 information entered by the site research team (i.e., see Section 3.2) and the site physician's clinical judgment, as noted below. During the study, ECP Treatment Cohort enrollees will receive protocol-based ECP therapy, whereas Observation Cohort enrollees will not receive protocol-based ECP unless they cross over subsequently to the ECP Treatment Cohort (see below).

Once eligibility is confirmed informed consent is obtained, FEV_1 values for the preceding 12 months (of which one FEV_1 must have been obtained within the preceding 14 days) will be entered into a web-based treatment allocation method which will perform an automated calculation of FEV_1 slope via the linear relationship of FEV_1 versus time, and determine if the rate of FEV_1 decline is statistically significant. Patients who have had a significant rate of decline within the preceding 6 months, defined as either a) for patients with $FEV_1 \geq 1200$ mL at the time of screening, a derived FEV_1 slope that is significantly lower (more negative) than -30 mL/month ($p < 0.05$); or b) for patients with $FEV_1 < 1200$ mL at the time of screening, a derived FEV_1 slope that is significantly lower (more negative) than -10 mL/month ($p < 0.05$), will be assigned to the ECP Treatment Cohort. If a patient does not meet these criteria, he/she will be assigned to the Observation Cohort. However, if a further decline in lung function is observed in refractory BOS patients in patients who do not meet these criteria, the site investigator may obtain up to 4 additional FEV_1 measurements (at intervals of no less than 7 days), and enter them into the web-based pulmonary evaluation form. Note for these Observation Cohort patients, further assessment of patient eligibility for treatment can be pursued via automated calculation every time each additional FEV1 value is entered. For refractory BOS patients in the observation Cohort, patients can be enrolled subsequently into the ECP Treatment Cohort if a) the rate and statistical significance of FEV_1 decline now meet the above criteria as confirmed by the web-based treatment allocation method using up to 4 ad-

ditional FEV_1 measurements ; b) the site physician requests that the patient receive ECP therapy; and c) the site research team confirms online that the patient has not developed a new contraindication to the use of ECP therapy. If the relationship between FEV_1 and time still does not reach statistical significance after the 4 additional FEV_1 measurements but there is strong clinical suspicion for progressive BOS, the physician may still enroll the patient into the ECP Treatment Cohort based on his/her clinical judgment ("clinical override"), provided that the rate of FEV_1 decline meets the above cut-off (-30 mL/month for patients with $FEV_1 \geq$ 1200 mL or -10 mL/month for patients with $FEV_1 <$ 1200 mL) and that the most recent FEV_1 was obtained within the preceding 7 days.

Patients who continue in the Observation Cohort but who experience a decline in pulmonary function may be re-evaluated for potential crossover into the ECP Treatment Arm after 2 months, using the above process and criteria, as long as at least one additional FEV_1 value is available within the preceding 7 days and provided the patient has not developed a new contraindication to the use of ECP therapy. Patients who cross over into the ECP Treatment Cohort will be followed for 1 year after the initiation of ECP.

3.6.2 Patients with Newly-Diagnosed BOS (Randomized Controlled Trial) Cohort

For eligible patients, site personnel will enter all available FEV_1 values into a web-based treatment allocation calculator which will confirm that the FEV1-related study eligibility criteria are met by performing an automated calculation of FEV_1 slope via the linear relationship of FEV_1 versus time to determine if the rate of FEV_1 decline meets the preset criteria i.e., a statistically significant (i.e., $p<0.05$) rate of decline of FEV1 that exceeds 30 mL/month. Patients whose FEV1 values meet these rate of decline within the either the preceding 6 months (i.e.,

in Patients monitored with Laboratory Spirometry) or 6 weeks (i.e., in Patients monitored with the Standardized Home Method Spirometry Method)[15],

will be consented and then randomized.

Prior to randomization, all patients with new BOS will be stratified based on the two following parameters:

1. their rate of decline at either $\leq$ 200 mL/month vs > 200 mL/month, respectively and
2. the Spirometry monitoring method used (either Laboratory-based or Home Spirometry); this stratification will be activated after IRB approval and implementation of the Standardized Home Spirometry Method.

Patients will then undergo strata-specific block randomization using a site specific random number table that will be provided by the DCC. Patients will be assigned to either **the Early Photopheresis Intervention (EPI) Arm** or to a **Control Arm**, and will receive a unique participant identification number. During the study, EPI Arm enrollees will receive protocol-based ECP therapy, whereas Control Arm enrollees will receive institution specific standard of care management of BOS and will not receive protocol-based ECP unless they cross over subsequently to the EPI Arm (see section 4.2 below).

If BOS is still suspected in a patient who does not initially meet the eligibility criteria, the site investigator may continue to evaluate the patient's eligibility using additional FEV_1 measurements (at intervals of no less than 14 days), and enter them into the web calculator.

3.7 Baseline and Pre-Treatment Assessments

---

[15] Patients who are being monitored with Home Spirometry and display a decline in FEV1 prior to either completion of the 2-4 week pre-monitoring period (i.e. to obtain the patient's normal range) or who develop a decline in lung function within 3 months of initiation of Home Spirometry Monitoring may be evaluated for eligibility using laboratory-based spirometry criteria.

Upon enrollment, each patient will be informed as to their specific treatment allocation.

For patients enrolled in the refractory BOS Registry, the patient will be notified as to their allocation to either the ECP Treatment Cohort or to the Observation Cohort (in which case he/she will not receive protocol-based ECP therapy but will be followed in the study to enable assessment of the FEV-1 based treatment allocation method).

For patients enrolled in the new BOS RCT Cohort, the patient will be notified as to their allocation to either the EPI Arm or to the Control Arm.

For all enrollees, patient demographics and co-morbidities should be entered on the Demographic/Medical History case report form. The post-transplant baseline FEV_1 (as defined by the standard ISHLT definition), and all FEV_1 measurements captured within the 6 months prior to enrollment, should be entered on the Confirmation of Eligibility case report form. The following laboratory and procedure related information will be recorded on the ECP Treatment case report forms for each patient treated with ECP after each individual procedure:

1. CBC with differential obtained the same day prior to each ECP treatment (for the second-day procedure of a consecutive-day pair, the previous day's CBC may be used) and the hemocytometer used for this measurement.
2. The type of machine used (UVAR vs CELLEX) and confirmation that either three to five cycles or 1500 mL of whole blood have been processed, respectively. If this did not occur, the reason why should be recorded along with the specific number of process cycles (UVAR) or volume (CELLEX).
3. The type and dose of anticoagulant used for the procedure (e.g. citrate vs heparin)

Within the Washington University site only, buffy coat product specimens will be obtained in a subgroup of patients on as many as three separate occasions to measure CBC with differential prior to photoactivation.

Important: a physician investigator or co-investigator must provide a signed Confirmation of Eligibility form that attests that the patient meets all eligibility criteria before ECP or any other study-related invasive procedure (e.g. central venous catheter placement) is performed.

4.0 TREATMENT DESCRIPTION

4.1 Allowed Medical Treatment

4.1.1. Maintenance immunosuppression (All Patients in both Registry and RCT)

Maintenance immunosuppressive regimens vary among transplant centers in the United States, but most patients are treated with triple-drug immunosuppression consisting of a calcineurin inhibitor (tacrolimus or cyclosporine A), a cell cycle inhibitor (mycophenolate mofetil or azathioprine), and prednisone. This research protocol does not require the use of a specific maintenance immunosuppressive regimen, and sites may choose specific regimens for patient-specific reasons. Changes in immunosuppression should be recorded monthly on the Change in therapy case report form. Similarly, infection prophylaxis protocols vary among centers, and participants may be treated according to local standard clinical practice. Patients may continue to receive their physician-prescribed treatments for other conditions. Women of childbearing potential in the ECP Treatment Cohort will be instructed to use an effective contraception method during their time in the trial, and will be instructed to notify the research team immediately if pregnancy occurs or if the contraceptive method fails in any manner.

4.1.2 Allowed Treatment for patients in Control Arm of RCT

Initial therapy for BOS will be dictated by the standard of care within each enrolling institution and will involve either changes (i.e., addition or deletions) in immunosuppressive agents or modification of respective medication doses and these patients will not be eligible to receive ECP treatment.

4.1.3 Allowed Treatment for patients in EPI Arm of RCT

Other than ECP, no other interventions for BOS will be used except for Azithromycin, measures in Section 4.1.1 and/or are consistent with Criteria 12 (Section 3.3) which may be administered in isolated patients pursuant to the discretion of managing clinicians. However, if agents that are commonly employed for BOS (e.g. steroids) are required as therapy for another non-BOS disorders (i.e., infections, allergic reactions etc.), their use or escalation will be allowed as long as they are consistent with Criteria 12 (Section 3.3).

4.2 Management of Crossover in Newly-Diagnosed BOS RCT

4.2.1 General Considerations for Crossover: Given the inexorable nature of BOS, crossovers must be allowed under certain circumstances to allow alternative therapy as a rescue option. However, if crossover between treatment arms is initiated too soon, it will affect the ability of the study to properly compare the primary efficacy endpoints between cohorts. Therefore, specific criteria will be used to guide the timing and requisite factors for rescue crossover for each cohort.

4.2.2. Crossover Criteria for RCT Patients who Experience "Treatment Failure"

For the purpose of guiding crossover decisions, **treatment failure** will be defined as less than a 50% decrease in the post-randomization rate of decline of FEV-1 compared with the rate of FEV-1 decline during the 6 months immediately prior to randomization. In general, patients may crossover to the other treatment arm at least six (EPI Arm) vs nine months (Standard Therapy Arm) after (or any time after nine months) treatment initiation, managing

clinicians suspect that a patient's BOS is continuing to progress and the patient meets the above definition of treatment failure. When a patient crosses over, the physician may institute whatever management is clinically indicated. For EPI Arm patients, completion of the 24 designated ECP treatment sessions is encouraged, if clinically indicated. To facilitate early detection of unresponsiveness to ECP therapy in EPI cohort patients and eligibility for crossover earlier than 9 months, rate of FEV1 decline will be calculated and provided to enrolling clinicians (i.e., to assess for treatment failure) for EPI patients six months after the first ECP treatment using three FEV1 values from months 4-6 after initiation of ECP to enable assessment for treatment failure pursuant to this requisite period of expected efficacy (see graph on page 12).

4.2.3 Early Crossover for RCT Patients who have or develop Accelerated Loss of Lung Function

A small minority of BOS patients demonstrate a particularly accelerated loss of lung function that exceeds 200 ml/month, and are at higher risk for early mortality.[10] Patients who are enrolled in the Severe BOS strata (i.e., pre-randomization rate of decline exceeding 200 mL/month) or who develop excessive FEV1 loss during a period of at least three months after treatment initiation (as shown by at least 3 FEV1s) will be allowed to crossover to the other treatment arm if their rate of FEV-1 decline 3 months after initiation of BOS treatment has not decreased by at least 50% compared with their pre-randomization rate of decline, AND IF they meet one of the following criteria:

1. Patients with FEV-1 < 1200 ml: initial[16] rate of FEV-1 decline exceeds 200 ml/month
2. Patients with FEV-1 < 1600 ml: initial[15] rate of FEV-1 decline exceeds 300 ml/month
3. Patients with FEV-1 < 2000 ml: initial[15] rate of FEV-1 decline exceeds 400 ml/month

[16] Initial refers to at enrollment

4.3 Extracorporeal Photopheresis (ECP)

Patients in the new BOS RCT (i.e., EPI Arm or in the Control Arm who have met criteria for crossover) or in the ECP Treatment Cohort of the Refractory BOS Registry should receive 24 ECP treatments over the 6-month period following enrollment, in accordance with the following schedule:

- 8 to 10 treatments over the first 30 days following treatment initiation;
- 8 to 10 treatments in the next 60 days (months 2 and 3);
- 6 treatments in the next 90 days (months 4 through 6) at a rate of 2 treatments per month.

Each treatment should be given on a separate day, and preferably two procedures should be completed in any given week during the first 5 weeks of therapy unless there are extenuating circumstances; treatments are scheduled more frequently early in the ECP treatment course to accelerate induction of the biological and clinical effects, and then are tapered over the remainder of the protocol. Therefore, it is important for enrolling centers to use their best efforts (i.e. minimize delays related to line insertion, scheduling conflicts, etc.) to complete the first 8-10 procedures within the 30 days and/or 12-14 procedures within 2 months especially for patients whose decline in FEV-1 exceeds 200 mL/month. At the physician's discretion, additional ongoing maintenance ECP treatments may be ordered following completion of the 6-month treatment course; in some instances, based on pulmonary function testing and other findings, the physician may stop, continue or reinitiate maintenance treatments on an indefinite basis. All ECP procedures performed over the first 12 months from initiation of therapy will be captured on the ECP Treatment case report forms.

ECP treatments will be performed using either the Therakos UVAR XTS system or the Therakos CELLEX system. Procedures should be performed in compliance with the FDA-approved

labeling for both of these systems (e.g. prerequisite criteria for minimum hematocrit; ≥30% if using UVAR XTS or ≥ 28% if using the Cellex for each procedure or for the initial procedure in a consecutive-day pair). The treatments should be performed using peripheral venous access whenever feasible (this is preferred, to avoid central venous catheter-related complications) or through a central venous catheter or pheresis-compatible implantable port, per the institution's standard practice. At any given time during the procedure, the extracorporeal volume (ECV) should not exceed 10% of the patient's estimated blood volume. Since the ECV can be influenced by the instrument used, cycle performed, and the patient's hematocrit, the physician should consult the specific device's Instructions for Use as needed.

A complete blood count with differential should be obtained and reviewed to confirm that the patient's hematocrit is at least 30% (UVAR procedures) or 28% (CELLEX procedures involving two needle access) before ECP is started (on the same day or on the previous day for a pair of consecutive-day procedures). At each treatment session, the patient should first be clinically assessed by the institution's clinical personnel to ensure that the patient is in suitable condition to undergo ECP that day. This assessment should include all the elements in the ECP Pre-Procedure Assessment Form in Appendix 4 - this Form should be completed for each ECP treatment session and filed in the patient's research binder at the site. If the pre-procedure assessment identifies any issues of concern, a physician or other licensed practitioner (e.g. physician's assistant or nurse practitioner) should assess the patient to determine if further clinical or laboratory investigations are required and ultimately to determine if ECP is safe to perform on that day or if the patient requires additional medical therapies prior to the start of ECP. Alternative institutional policies for pre-procedure ECP assessment may be followed if reviewed and approved by the Washington University Principal Investigator. Treatments may be postponed or cancelled altogether at the treating physician's discretion if the patient develops a medical contraindication to ECP therapy; however, the reason must be

documented. Patients should be monitored for complications in accordance with local standard practice and should be instructed to avoid sun exposure for 24-48 hours after each ECP treatment (ideally) and to wear hats, protective clothing, sunscreen, and UV-resistant sunglasses if sun exposure will occur within the first 24-48 hours after an ECP treatment.

5.0 STUDY OUTCOMES AND FOLLOW-UP

5.1 Primary endpoints:

5.1.1. Refractory BOS Registry*:* Pursuant to our analysis of data from a subset of patients enrolled in the current study (see graph on page 12), the primary endpoint of the study now involves a change in the rate of FEV_1 decline assessed by comparing the average rate of FEV_1 decline over the 6 months prior to ECP against the average rate of FEV_1 decline over the 12 months following initiation of ECP. A clinical response will be defined as a 50% or greater reduction in the rate of decline of FEV1 before and after the ECP.

5.1.2. Newly-Diagnosed BOS RCT Cohort: Two primary endpoints will be compared between the two arms in the randomized controlled cohort as follows:

1. Survival: Our hypothesis is that patients in the EPI Cohort will experience a 25% reduction in mortality three years after randomization compared with patients in the Control Cohort.
2. Rate of decline of Lung Function: A 25% or greater difference in the percentage of patients within each of the two cohorts (Control vs EPI) who achieve a clinical response as defined previously (i.e., 50% or greater reduction in the rate of FEV_1 decline as assessed by comparing the average rate of FEV_1 decline over the 6 months prior to ECP against the average rate of FEV_1 decline over the 12 months following randomization).

5.2 Secondary endpoints:

All PATIENTS:

A) Average rate of FEV_1 decline over the 9 months following initiation of ECP (i.e., in the refractory Cohort) or randomization (i.e., in the RCT cohort);

B) All-cause mortality annually for five years following either randomization (RCT) or initiation of ECP in patients with refractory BOS (Registry – observational only);

C) Proportion of patients with treatment-related serious adverse events after randomization (RCT) or after ECP initiation (Registry).

D) Within subject change in health quality of life (QOL) from baseline (enrollment up to the first ECP treatment) at months 3, 6, 9 and 12 and annually up to five years. QOL assessments will be made using multiple surveys.

REFRACTORY BOS PATIENTS

E) For the Refractory BOS Registry, additional analyses will be performed to evaluate the validity of the study's FEV_1-based treatment allocation method using data from enrollees in both Arms who do not meet these criteria as defined in Section 6.0.

RCT PATIENTS:

F) A 30% increase in residual (i.e., at six months after randomization) FEV1 values in BOS treatment ARM (EPI or Control) patients; this would include all patients.

G) Incidence of pulmonary specific, CVC related and all infections between RCT arms

H) Hospitalization rates between RCT arms

I) Treatment related SAEs between RCT arms

5.3 Pulmonary Function Testing

Spirometry should be routinely measured at all clinical centers by certified and trained technicians according to American Thoracic Society (ATS) guidelines. According to ISHLT criteria, baseline lung function is defined as the average of the two highest FEV_1 measurements obtained following transplantation, taken at least 3 weeks apart. This baseline is used as the reference value for the diagnosis and staging of BOS (Table 1 on page 3).

Additionally, participating sites will capture and report all FEV_1 measurements during the 12 months prior to enrollment, inclusive of an FEV_1 measurement on Day 0, where Day 0 is defined as the period within one week prior to, and/or on the date of, initiation of ECP. However, it is preferable to measure the Day 0 FEV-1 within 24-48 hours prior to the first ECP procedure. The five FEV1 measurements obtained in the six month period prior to enrollment should not be measured in an interval less than two weeks apart. These FEV_1 values obtained prior to initiation of ECP will be used to calculate an average pre-ECP rate of change in FEV_1 in mL/month as described below in the Data Analysis section.

In ECP Treatment enrollees, the study will prospectively capture FEV_1 through spirometry during the course of ECP therapy and out to one year in accordance with the following schedule: Days 0, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330 and 365. Spirometry from Day 0 through Day 90 may be performed within ±7 days to accommodate patient/provider scheduling needs, and generally will coincide with a scheduled ECP treatment. Spirometry from Day 91through Day 180 may be performed within ±14 days to meet patient/provider scheduling needs. Spirometry from Day 181 through Day 365 may be performed within ±30 days to meet patient/provider scheduling needs. Oxygen saturation measurements should be recorded at every Spirometry session day. Observation Cohort enrollees should be followed for the duration of the study's follow-up period, but may have the timing of pulmonary func-

tion testing determined by their local physicians. For Observation Cohort enrollees, the results of all clinically-ordered pulmonary function tests should be collected and reported on the case report forms.

5.4 Health-Related Quality of Life

For chronic conditions like BOS, assessment of health-related QOL yields information on patient-important outcome beyond that obtained by clinical examination or physiological assessments. QOL is measured from the patient's perspective, which enables evaluation of a condition's impact on patients' health and daily functioning. Generic measures allow comparison across different conditions, while disease-specific measures are more responsive to treatment effects in patients with the same disease. In the New BOS RCT, we will assess QOL at baseline and at 3 months, 6 months, 9 months, 12 months, and annually out to 5 years using the following measures: a) generic QOL: EQ5DL (takes 1-2 minutes to complete); and b) respiratory-specific QOL: MMRC (1 minute), D12 (2 minutes), SGRQ-C (10-15 minutes).

5.5 Subject Retention, Withdrawal, and Termination

To promote continued participation, trial staff will provide telephone reminders to patients of study visits. Subjects will be encouraged to remain in the trial until follow-up is complete but will be informed that they have the right to withdraw at any time without compromise to their care. Subjects will be terminated from the trial if they die or elect to withdraw. If a patient scheduled for ECP Treatment exhibits improvement in FEV-1 after enrollment but before ECP is initiated, he/she should continue to be followed in the trial but ECP treatment may be delayed or avoided at the physician's discretion.

6.0 ADVERSE EVENT MONITORING AND REPORTING

6.1 Adverse Event (AE) Definition

An Adverse Event is defined as any untoward medical occurrence observed in a patient that develops or worsens from baseline status in association with a subject's participation in the research, whether considered research-related or not.

6.2 Serious Adverse Event (SAE) Definition

A Serious Adverse Event is any AE that results in death, a life-threatening adverse experience, a persistent or significant disability/incapacity, inpatient hospitalization or prolongation of existing hospitalization, evaluation in an emergency room or by an acute response team, pregnancy abortion, or a congenital anomaly, birth defect, or cancer in a neonate/infant born to a female subject. Medical events that do not strictly fulfill these criteria should be considered SAEs if they seriously jeopardize the subject or require aggressive medical or surgical intervention to prevent one of the above outcomes.

6.3 Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the trial. Such conditions should ideally be reported in the baseline medical/surgical history. A pre-existing medical condition should be reported as an AE or SAE only if the frequency, severity, or character of the condition worsens significantly or unexpectedly during the trial. Previously scheduled hospitalizations and hospitalizations needed for diagnostic or elective surgical procedures for the management of pre-existing conditions are not considered AEs.

6.4 Reporting of AE and SAE

Patients will be monitored and followed clinically according to each site's standard clinical practice. Sites should follow their local IRB's guidelines in terms of reporting AEs and SAEs to the local IRB. In addition, each SAE should be categorized by the site investigator as to whether it was related or possibly related to participation in the research study (meaning that there is a reasonable possibility that the AE may have been caused by study participation

- SAEs determined to be solely caused by an underlying disease, disorder, or condition of the subject; or other circumstances unrelated to the research should be categorized as not related to participation in the research).

SAEs that a) are fatal or imminently life-threatening; or b) are felt by the site investigator to be related or possibly related to the use of ECP, to methoxsalen, or to a central venous catheter that was placed for the purpose of performing ECP; or c) occur during or within six hours after an ECP procedure must be reported to the Data Coordinating Center (DCC) on the SAE Case Report Form, and source documentation provided, within 24 hours (Monday-Friday) of the site's awareness of the event. Each SAE that qualifies for reporting to the DCC should also be categorized by the site investigator as to whether it was unexpected (meaning that the SAE's occurrence is not consistent with the known or foreseeable risks associated with the study treatments or with the expected natural progression of any underlying disease, disorder, or condition of the subject and his/her predisposing risk factor profile for the SAE), or expected. An SAE is not considered officially reported to the CCC until the SAE form is submitted online. The final SAE must be signed and dated by the PI and submitted online.

FOR RCT PATIENTS: For purposes of monthly review of SAEs between treatment arms by the DSMB and Medical Monitor, SAEs will be summarized in various disease specific categories (e.g. cardiac, neurologic, renal, hepatobiliary, hematologic, infection) and whether or not they require either an ED visit, hospitalization or result in mortality. Monthly reports comparing the incidence of these SAEs and their effects within each treatment arm will be provided to the DSMB for review.

6.5 Expedited Review of ECP-Related, Fatal, or Life-Threatening SAE

At the DCC, each SAE report will be forwarded to the Principal Investigator or a physician designee. If additional details are needed to evaluate the event, this will be conveyed to the site

research team. For ongoing events, the Principal Investigator will communicate any suggestions relevant to the patient's care to the site investigator. Each reported SAE will be reviewed by the DSMB or Medical Monitor; this will occur within 3 business days (Monday – Friday) for any SAE that is either a) categorized as related or possibly related to ECP; or b) fatal or imminently life-threatening. Any DSMB or Medical Monitor recommendations pertaining to the specific event, event categorization, or study site processes will be forwarded to the site investigator. Should an event be determined to qualify as an Unanticipated Problem, federal reporting guidelines will be followed. Stopping guidelines will be established in advance to guide the DSMB with respect to halting enrollment at either a specific center or at all participating study sites. If the DSMB stops enrollment, all site investigators will be notified. It will be the investigators' responsibility to notify their respective local IRBs.

7.0 STATISTICAL METHODS, POWER CALCULATIONS AND ENROLLMENT ESTIMATES

7.1 Refractory BOS Registry Cohort

7.1.1 Rate of FEV1 Decline Primary Outcome

Initial Enrollment Projections: Based on a 95% power analysis and assuming a 5% loss to follow-up of enrolled patients, 160 patients who meet the pre-enrollment FEV-1-stratified slope cutoffs and statistical significance criteria specified in Section 3.6 will need to be enrolled in the ECP Treatment Cohort to detect at least a 50% reduction in the rate of FEV_1 decline at one-year follow-up. Because we anticipate from our prior study that a maximum of 12% of enrolled patients will not meet these criteria, we initially planned to enroll up to 182 patients in total (including the enrolled patients under Observation). A 50% decrease in the rate of FEV_1 decline can importantly extend survival and improve the opportunity to receive a new lung allograft, as well as delay time to onset of severe physical limitations. Our power analysis was based on findings from our previously published 60 patient series. Specifically,

we first calculated values that reflected the difference between pre-intervention and post-intervention FEV_1 slope values. The corresponding values for standard deviation of slope differences were adjusted for possible greater variability in the post-treatment period in this study. These values for derived slope differences (50% of 87 ml/month) and corresponding standard deviation values (150) were then used to calculate required enrollment using a treatment effect of 50% reduction of FEV_1 decline and using a power of 95%. This analysis, with 5% late loss, indicates a required enrollment of 160 patients who receive ECP and meet the FEV-1 criteria in Section 3.2.1. Although 160 patients had been originally scheduled to enter into the ECP Treatment Cohort (by new enrollment or crossover), an additional 80 patients will now be enrolled into the ECP Treatment Cohort pursuant to section 7.3 and the observed increase in early mortality described on page 10 (for a total of 240 patients to enter the Treatment Cohort, 273 will have to be enrolled).

7.1.2. Enrollment Projections for Refractory BOS Registry

Based on experience over an 8-year period at Barnes-Jewish Hospital, approximately 13% of patients receiving a lung transplant eventually received ECP. Roughly one-half of post-transplant patients do not develop BOS, and a substantial proportion of those patients who do develop BOS die from complications of infection or other causes. To develop a projected enrollment for patients within the refractory BOS Registry over our proposed four-year study period, we had previously applied the following assumptions:

- There will continue to be ~1,800 lung transplants performed yearly in the U.S.;
- Roughly 13% of post-transplant patients will eventually receive ECP treatment;
- Providers managing roughly 40% of U.S. lung transplants will refer their drug-refractory BOS for ECP (it is uncertain what share will actually do so); and

- Medicare beneficiaries are as likely to receive ECP therapy as non-Medicare patients and account for ~50% of qualifying candidates for ECP therapy.

Applying these assumptions, we estimated annual patient enrollment as follows:

1,800 transplants x 13% ECP TX rate x 40% participation rate x 50% Medicare = ~50 patients/year

In actuality, we had a reasonable enrollment of 44 patients over one year despite the fact that we only had an average of less than 10 centers enrolling patients during that interval. To enroll 160 patients required to detect a 50% reduction in the rate of FEV_1 decline, it was anticipated that enrollment may be required for approximately three years based on this 50-patient-per-year projection. An additional year will be required to complete one-year follow-up on the last patients enrolled.

7.1.3. Revised Enrollment Projections for Refractory BOS Registry

Based on the substantial increase in early (i.e., 32%) and one year (41%) mortality observed in the first 44 patients enrolled, the enrollment projection will be increased by 50% (i.e., n=240) for patients with refractory BOS. To accomplish this, it is anticipated that enrollment may be required for approximately four and one half years based on this 50-patient-per-year projection. The patient will be followed for the sooner of five years or until their date of death and the following data will be collected annually after the first year: Spirometry results, the number of maintenance ECP treatments performed will be tabulated and QOL surveys for up to five years.

7.1.4. General Considerations for the Refractory BOS Registry Cohort

Because this is a before-and-after Registry study in which enrolled subjects serve as their own controls, the heterogeneity of the study population will not influence overall study out-

come. However, as described in the Data Collection, Analysis and Reporting section below, seven specific parameters for which there is a rational basis to potentially influence clinical outcome will be independently evaluated by univariate and multivariate linear and logistic regression analysis.

There are no restrictions in the study inclusion or exclusion criteria with respect to gender or minority status (e.g. race or ethnicity); thus enrollment will reflect the gender and racial/ethnic mix of patients enrolled in all participating study sites. In our previous single-center analysis of 60 patients, males and females were about equally represented (males: 53%; females: 47%); we anticipate roughly similar gender mix in this multicenter registry study. The small 240 subject enrollment sample effectively precludes a conclusive sub-analysis of any possible effect of race or ethnicity on clinical outcome; however, the heterogeneity should be diverse based on enrollment from multiple centers in several geographic areas within the United States.

It is difficult to project annual patient enrollment, in part because there are currently multiple barriers to ECP therapy for post-lung transplant BOS, most prominently the historical lack of Medicare coverage and payment. We expect that this Study, with Medicare coverage and payment for qualifying patients, will expand utilization of ECP to include more centers and a higher proportion of the eligible patient population.

7.2. Newly-Diagnosed BOS Randomized Controlled Trial Cohort

7.2.1. Enrollment Projections for RCT

7.2.2 Assumptions:

To develop a projected enrollment for patients in the RCT, we apply the following assumptions:

- Annual Transplant Volume within 18 enrolling centers of 791
- Estimated Annual Transplant Volume within our 20 enrolling centers of 1062
- Estimated BOS Surveillance population within our 20 enrolling centers of 7079
- Percentage of surveillance population without previous BOS of 70%
- Percentage of eligible patients with Medicare of 43%
- An annual new BOS rate of 7.5%
- Enrollment target of 60-80% of BOS surveillance population

7.2.3. Enrollment Projections

Applying these assumptions, we estimated annual patient enrollment as follows:
7079 surveillance patients x 70% with new BOS x 43% CMS patients x 7.5% BOS rate x 80% enrollment rate = ~128 patients/year and at 60% enrollment rate = ~96 patients/year. The duration of this trial will be predicated on the enrollment rate which may be influenced by a number of factors that are out of the control of the Sponsoring Center. We estimate that a minimum of six to 12 months will be required to tabulate and analyze all data for submission to CMS for its review.

7.3 POWER CALCULATIONS

7.3.1. Rate of FEV1 Decline Primary Outcome

A clinical response will be determined using an FEV_1 primary endpoint and will be defined as a 50% or greater reduction in the rate of decline of FEV_1 assessed by comparing the average rate of FEV_1 decline over the 6 months prior to ECP against the average rate of FEV_1 decline over the 12 months following initiation of ECP. To detect a 25% difference in the percentage of patients who achieve a clinical response to therapy (i.e., 50% decrease in the rate of FEV_1 decline when comparing slope values before and 12 months after ECP therapy) between the

two randomized patient arms who meet the standardized criteria for BOS, 452 patients will be required (using 95% power). An enrollment of 542 patients is projected based on an attrition rate related to either early crossover (15%) or loss to follow-up (5%). The outcomes between the two BOS disease severity strata will be assessed separately. The power analysis was based on data obtained from our previous publication[17] in which 68% of patients had achieved this endpoint (i.e., a 50% or greater reduction in rate of decline in FEV_1); therefore, we performed the power analysis using a difference that would exceed 17% between the two patient groups (i.e., 68% in the EPI group and 51% in the control group).

7.3.2. Survival Primary Outcome

Mortality three years after diagnosis of BOS using standard of care management of BOS is 52%. This value was obtained by averaging the 3 year mortality from four previous publications[18,19,20,21] that summarized mortality at three years after BOS diagnosis. To detect at least a 25% reduction in mortality (i.e., from 52 to 39%) between the two randomized cohorts who meet the standardized criteria for BOS, 616 patients would be required (using 90% power). Assuming 15% exclusion related to early crossover and a 5% loss to follow-up of enrolled patients, 739 patients who meet the standardized criteria for BOS would need to be enrolled and randomly assigned to either the EPI or control cohorts to detect a difference. The outcomes between the two BOS disease severity strata will be assessed separately. Therefore, it

[17] Morrell MR, Despotis GJ, Lublin DM, et al. The efficacy of photopheresis for bronchiolitis obliterans syndrome after lung transplantation. *J Heart Lung Transplant* 2010 Apr;29(4):424-31.
[18] Finland Copeland CA, Snyder LD, Zaas DW et al. Survival after Bronchiolitis Obliterans Syndrome among Bilateral Lung Transplant Recipients. Am J Respir Crit Care Med 2010;182:784-89.
[19] Morrell MR, Despotis GJ, Lublin DM, et al. The efficacy of photopheresis for bronchiolitis obliterans syndrome after lung transplantation. *J Heart Lung Transplant* 2010 Apr;29(4):424-31.
[20] Todd JL, Jain R, Pavlisko EN et al. Impact of Force Vital Capacity Loss on Survival after the Onset of Chronic Lung Allograft Dysfunction Am J Resp Crit Care Med 2014;189:159-166.
[21] Belloli EA, Wang X, Murray S et al. Longitudinal Force Vital Capacity Monitoring as a Prognostic Adjunct after Lung Transplantation. Am J Resp Crit Care Med 2015;192:209-18,

is anticipated that a period of approximately either 4.7 years based on a 100% enrollment rate, 5.9 years based on an 80% enrollment rate or 7.9 years based on a 60% enrollment rate will be required. An additional five years will be required to complete a five-year follow-up for mortality on the last patients enrolled. The patient will be followed for the sooner of up to five years or until their date of death and the following data will be collected annually after the first year: Spirometry results, the number of maintenance ECP treatments performed will be tabulated and QOL surveys.

8.0 DATA COLLECTION, ANALYSIS, AND REPORTING

A Data Coordinating Center (DCC) will manage implementation of the trial and provide bio statistical expertise for data capture, spreadsheet entry, and analysis. The DCC will develop case report forms (CRFs) to collect trial-related data through a secure web-based data entry system. These case report forms will be approved by the study Steering Committee. Individual clinical sites will be responsible for electronic data entry, and the DCC will provide training and support for the use of the electronic data entry system.

CRFs will be created as trial-specific web forms linked to a central database. To minimize text entry errors, most of the data fields for each CRF only allow the user to select a radio button, check box, drop down menu, or electronically checked numeric data entry. To reduce missing data, CRFs will be constructed so they must be filled out completely before the system will allow submission. DCC staff will spot check incoming data to check for accuracy and completeness. A preliminary set of data fields for inclusion in CRFs are available for review upon request.

Initial analyses will involve the use of descriptive statistics. To compare baseline characteristics between subgroups, we will use t-tests (or a non-parametric test) and chi-square (or

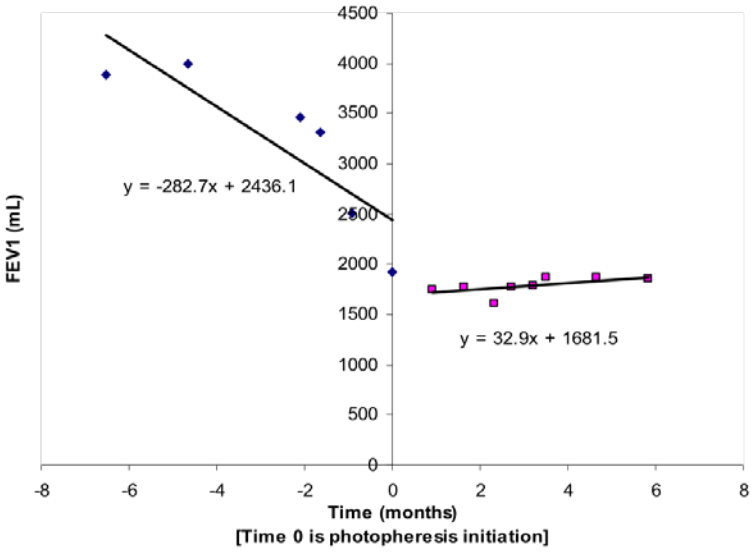
Fisher's exact) tests. For comparisons among subgroups, we will use ANOVA or chi-square (or Fisher's exact) tests.

We will analyze the rate of change in FEV_1 using two methods. First, absolute values of all FEV_1 measurements obtained over the 6 months before the initiation of ECP will be collected retrospectively at study enrollment, and absolute values of all FEV_1 measurements obtained over the 12 months after the initiation of ECP will be collected prospectively. A rate of change in FEV_1 will be obtained by plotting absolute FEV_1 measurements vs. time, and a linear regression line will be drawn through these data points (example in Figure 3 next page). The rate of change in FEV_1 will be defined for each time period as the slope of this linear regression line, and the pre-ECP slope will be compared to the post-ECP slope for each patient using the paired t-test as recommended by the ISHLT consensus statement on BOS. In addition, changes in FEV_1 measurements in the different time periods (pre-ECP and post-ECP) will be analyzed using longitudinal mixed-effects models analysis of variance.

Although comparisons will be made on the ITT population of patients with new BOS, the primary outcomes will be analyzed using the strata of patients who do not have severe BOS (i.e., < 200 mL/month loss of FEV1). Oneway analysis of variance will be used to compare each of the two primary endpoints between patients within the two cohorts (i.e., Control and EPI) enrolled in the RCT arm of the trial: 1. the percentage of patients who meet of the criteria for spirometry based clinical response to therapy (i.e., 50% reduction in the rate of decline of pulmonary function when comparing rate of decline just prior to and six months after implementation of either standard of care or ECP therapy) 2. Survival from time of BOS diagnosis will be compared annually between the two cohorts during the course of the trial. We will use the Kaplan-Meier method to estimate survival and the log rank test to compare survival between BOS treatment cohorts and all patient subgroups. Multivariate cox regression anal-

ysis using time dependent covariates will be used to analyze survival benefits of the treatment cohorts and the influence of potential confounders such Spirometry monitoring method used (i.e., Home vs laboratory based Spirometry).

Figure 3. Example of linear regression-based development of rates of FEV1 decline for the six-month period prior to and following initiation of ECP



Parametric (e.g. one-way or ANOVA analysis of variance), non-parametric (e,g, rank sum) and univariate and multivariate linear and logistic regression statistical methods will be used to characterize response and non-response and examine the potential association of one or more of several parameters with either response or non-response to ECP treatment. These parameters will include (1) Day 0 (pre-ECP) percent of post-transplant baseline FEV_1, (2) age, (3) race, (4) days from transplantation to initiation of ECP treatment, (5) individual use or non-use of calcineurin inhibitor, cell-cycle inhibitor, steroids, sirolimus or everolimus as

components of maintenance immunosuppression, (6) history of gastroesophageal reflux disease (GERD) with and without active treatment and (7) single- or double-lung transplant status. All variables that are significant using univariate analyses will be included in multivariate analyses.

By nature this is a very heterogeneous population, in which declining pulmonary function may be influenced by numerous underlying demographic, co-morbidity and treatment-related factors. The very limited potential enrollment size for the Registry component of this revised study and the direct consequence of a very small qualifying post-lung transplant patient population with treatment-refractory BOS precludes the possibility of enrolling enough patients to assure that risk factors for pulmonary function decline are similar.

Quarterly interim status update reports will be submitted electronically by the trial sponsor to CMS (Kimberly.Long@cms.hhs.gov) that contain the following information: (1) number screened, (2) number enrolled, (3) reason for non-enrollment, (4) number of dropouts and reason for dropout, (5) number with completed data collection, (6) progress of data analysis, (7) analysis file constructed (y/n), (8) descriptive analysis completed, (9) analyses to address each hypothesis completed (y/n), (10) manuscript completed (y/n) and (11) manuscript sent to journal (date). Study data analysis will be initiated upon completion of enrollment and one year of treatment of all trial subjects.

9.0 DATA CONFIDENTIALITY

The following precautions will be taken to ensure privacy of patient data:

1. The trial will be conducted in accordance with the Health Insurance Portability and Accountability Act (HIPAA).
2. Personal identifiers will not be entered in the electronic database (this data will be stored in a secure location at the clinical center with restricted access), and will be

removed from all patient material sent to the DCC (e.g. source documents). Data will be identified using unique Participant Identification Numbers that provide no subject information.

3. Clinical centers will require a complex password to gain access to web-based documents. Authentication (user credentials) and access privileges will be managed by DCC staff using proven, industry standard tools.
4. The DCC database will be password protected with strong encryption and will be hosted in a private cloud infrastructure managed by the DCC. The database server will be attached to a private network protected by a commercial grade firewall.
5. All attempts to access the DCC database will be logged.
6. All data-related practices will comply with Washington University policies and procedures for privacy and data security.
7. At the clinical centers, subject data will be kept in a locked office and on password-protected and firewall-protected computer systems, and will only be available to the research team. Different password-protected files will be created and will be linked using the patient's unique Participant Identification Number. Subject identifiers will be kept separate from study data, with the identifier keys stored in separate files which only the site principal investigator and authorized personnel can access.

10.0 INVESTIGATOR TRAINING AND STUDY OVERSIGHT

Project personnel will have the appropriate qualifications related to education, training, and experience to perform trial-related tasks. The trial personnel will conduct the trial in accordance with Good Clinical Practice (GCP) and local IRB guidelines. The protocol will require local IRB approval before its implementation. Clinical site personnel will obtain written informed consent from trial participants before conducting trial-related procedures. Site per-

sonnel are required to notify the Washington University Clinical Coordinating Center of any deviation from the IRB-approved protocol within 24 hours of their awareness.

The DSMB will consist of an independent group of three experts (comprising a pulmonologist with expertise in management of post-lung transplant BOS, a specialist with photopheresis procedural experience and a biostatistician) who will periodically review (every 6 months) and evaluate the accumulated data for participant safety, trial conduct and progress, and make recommendations to the trial Steering Committee (i.e., consisting of Medical Monitor, DSMB chairman and PI) regarding the continuation, modification, or termination of the trial. A physician with expertise in the management of post-transplant BOS (either the chairperson of the DSMB or another designated person) will serve as the Medical Monitor for this project. Per the DSMB, the trial may be terminated if there are safety concerns or the accumulated data provide compelling evidence of improved survival in either group. Mandatory reviews of study data will be scheduled following enrollment and accrual of six months of ECP treatment data for (1) the first 50 and (2) the first 100 patients and then on an annual basis to assess the impact of the EPI intervention on patient safety and enhanced survival; pursuant to approval of our DSMB, the trial will be terminated if the survival endpoint is achieved or exceeded (i.e., > 25% reduction in mortality in the EPI Arm) at any annual interim analysis or at the discretion of the DSMB related to substantial safety concerns.

Study monitoring visits will be conducted by authorized representatives of the Principal Investigator to inspect study data, informed consent forms, and subjects' medical records. The clinical center investigator will permit authorized representatives of Washington University and federal and local health authorities to inspect relevant facilities and records.

11.0 TRIAL TIMELINE

We expect to conduct this trial over a minimum 6 year period that will include study start-up tasks, assembly of a DSMB, and central and local IRB approvals. We plan to enroll and treat patients over about 6-7 years, with a long term follow-up on the last enrolled patient (see section 7.3). At least 6-12 months of additional time will be necessary to complete data acquisition and analysis.

Appendix 1: FDA IND WAIVER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 118030

ACKNOWLEDGE/EXEMPT IND

George J. Despotis, MD
Washington University School of Medicine
660 S. Euclid Avenue
Campus Box 8118
St. Louis, MO 63110-1093

Dear Dr. Despotis:

We acknowledge receipt of your Investigational New Drug Application (IND), submitted March 4, 2013, received March 5, 2013, under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA) for UVADEX (methoxsalen).

After reviewing the information contained in your submission, we have concluded that your study titled "Extracorporeal Photopheresis (ECP) for the Management of Progressive Bronchiolitis Obliterans Syndrome (BOS) in Medicare-Eligible Recipients of Lung Allografts" meets all of the requirements for exemption from the IND regulations and, therefore, an IND is not required to conduct your investigation. In accordance with 21 CFR 312.2(b)(4) of the regulations, FDA will not accept your application.

The IND regulations [21 CFR 312.2(b)] state that the clinical investigation of a drug product, including a biological product, that is lawfully marketed in the United States, is exempt from the requirements for an IND if all of the following apply:

1. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use, nor intended to be used to support any other significant change in the labeling for the drug.

2. The investigation is not intended to support a significant change in the advertising for a prescription drug product.

3. The investigation does not involve a change in route of administration, dosage level, or patient population, or other factor that significantly increases the risks (or decreases the acceptability of risks) associated with use of the drug product.

4. The investigation is conducted in compliance with the requirements for institutional review (21 CFR Part 56) and informed consent (21 CFR Part 50).

Reference ID: 3278962

5. The investigation is conducted in compliance with the requirements of 21 CFR 312.7, i.e., the drug may not be represented as safe or effective, nor may it be commercially distributed, for the purposes for which it is under investigation.

In addition, 21 CFR 312.2(b)(5) exempts from the IND requirements a clinical investigation that involves use of a placebo if the investigation does not otherwise require submission of an IND.

We remind you that exemption from the requirements for an IND does not in any way exempt you from complying with the requirements for informed consent under 21 CFR 50.20 or from initial and continuing Institutional Review Board review under 21 CFR Part 56. You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 U.S.C. §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. Please note that, if in the future you submit an application under sections 505, 515, or 520(m) of the FDCA (21 USC §§ 355, 360(e), or 360(j)(m)), or under section 351 of the PHS Act (21 U.S.C. § 262), or you submit a report under section 510(k) of the FDCA (21 USC § 360(k)), the application or submission must be accompanied by a certification that all applicable requirements of section 402(j) of the PHS Act (42 USC § 282(j)) have been met. Where available, such certification must include the appropriate National Clinical Trial (NCT) control numbers (42 USC § 282(j)(5)(B)). Additional information regarding the certification is available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information on registering your clinical trial(s) is available at the Protocol Registration System website (http://prsinfo.clinicaltrials.gov/).

For additional information, a searchable version of the IND regulations is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm.

If you have any questions, call Judit Milstein, Chief, Project Management Staff at 301-796-0763,.

Sincerely,
{See appended electronic signature page}

Renata Albrecht
Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Reference ID: 3278962

Appendix 2: FDA WAIVER CONTINUATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 118030 ADVICE

George J. Despotis, MD
Washington University School of Medicine
660 S. Euclid Avenue
Campus Box 8118
St. Louis, MO 63110-1093

Dear Dr. Despotis:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for UVADEX (methoxsalen), and to our correspondence dated March 20, 2013, where we granted an exemption from requirement of an IND for your study titled "Extracorporeal Photopheresis (ECP) for the Management of Progressive Bronchiolitis Obliterans Syndrome (BOS) in Medicare-Eligible Recipients of Lung Allografts."

We also refer to your correspondence dated December 15, 2016, where you request confirmation that a proposed amended protocol which includes a randomized, controlled cohort with first line use of UVADEX/photosphere is still exempt from the IND requirements.

After reviewing your revised protocol we have concluded that your amended study titled
"Extracorporeal Photopheresis (ECP) for the Management of Progressive Bronchiolitis
Obliterans Syndrome (BOS) in Medicare-Eligible Recipients of Lung Allografts" meets all of the requirements for exemption from the IND regulations. Therefore, an IND is not required to conduct your investigation.

The IND regulations [21 CFR 312.2(b)] state that the clinical investigation of a drug product, including a biological product, that is lawfully marketed in the

United States, is exempt from the requirements for an IND if all of the following apply:

1. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use, nor intended to be used to support any other significant change in the labeling for the drug.

2. The investigation is not intended to support a significant change in the advertising for a prescription drug product.

3. The investigation does not involve a change in route of administration, dosage level, or patient population, or other factor that significantly increases the risks (or decreases the acceptability of risks) associated with use of the drug product.

4. The investigation is conducted in compliance with the requirements for institutional review (21 CFR Part 56) and informed consent (21 CFR Part 50).

5. The investigation is conducted in compliance with the requirements of 21 CFR 312.7, i.e., the drug may not be represented as safe or effective, nor may it be commercially distributed, for the purposes for which it is under investigation.

In addition, 21 CFR 312.2(b)(5) exempts from the IND requirements a clinical investigation that involves use of a placebo if the investigation does not otherwise require submission of an IND. We remind you that exemption from the requirements for an IND does not in any way exempt you from complying with the requirements for informed consent under 21 CFR 50.20 or from initial and continuing Institutional Review Board review under 21 CFR Part 56. You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the
Public Health Service Act (PHS Act) (42 U.S.C. §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. Please note that, if in the future you submit an application under sections 505, 515, or 520(m) of the FDCA (21 USC §§ 355, 360(e), or 360(j)(m)), or under section 351 of the PHS Act (21 U.S.C. § 262), or you submit a report under section 510(k) of the FDCA (21 USC § 360(k)), the application or submission must be accompanied by a certification that all applicable requirements of section 402(j) of the PHS Act (42 USC § 282(j)) have been met. Where available, such certification must include the appropriate National Clinical Trial (NCT) control numbers (42 USC § 282(j)(5)(B)). Additional information regarding the certification is available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/uc m095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information on registering your clinical trial(s) is available at the Protocol Registration System website (http://prsinfo.clinicaltrials.gov/).

We further remind you that exemption from the requirements for an IND does not exempt you from complying with the requirements under 21 CFR Part 812 (Investigational Device Exemptions (IDE)) if your study includes use of a device for purposes of making critical treatment decisions, e.g., as an inclusion criterion or to assign a subject to a treatment arm or dose. The sponsor is responsible for determining whether submission of an IDE application to FDA is required before a study may proceed. If you are unsure of whether an IDE is required, you may contact your local IRB to aid in this determination, and may also contact the Center for Devices and Radiological Health (CDRH) at 301-796-5450 or the Center for Biologics Evaluation and Research (CBER) (if the device is for an HIV or HLA matching test) at 301-827-1800. If you determine that a submission of an IDE is not required, the IRB must review that determination.

For additional information about IND regulations, you can check our web site at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm

If you have any questions, call Judit Milstein, Chief, Project Management Staff at 301-796-0763.

Sincerely,

{See appended electronic signature page}

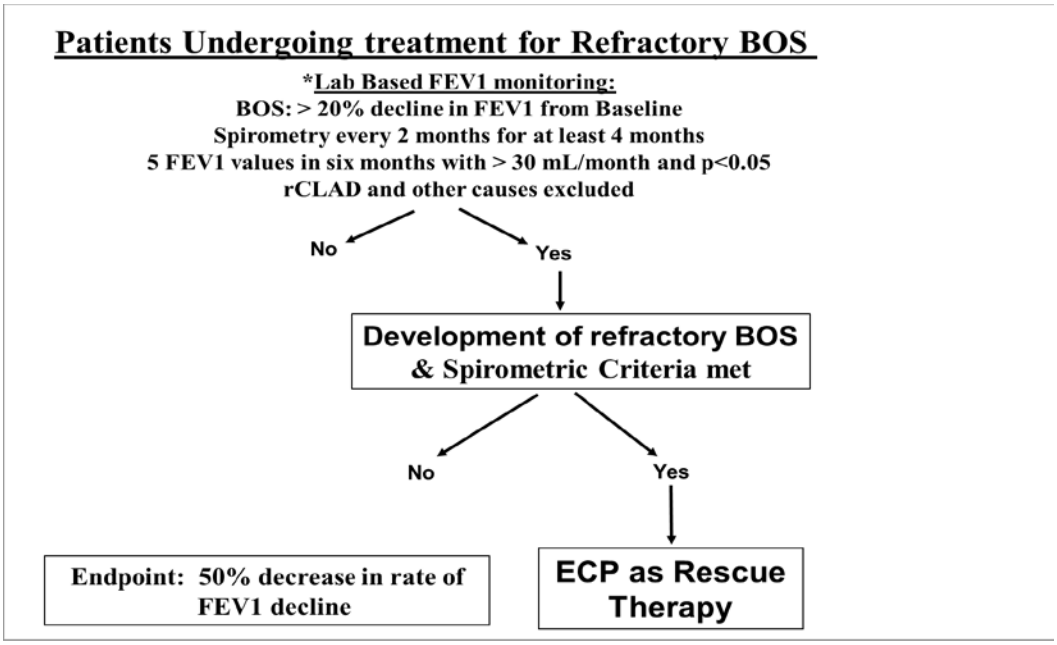
Renata Albrecht, MD
Director
Division of Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

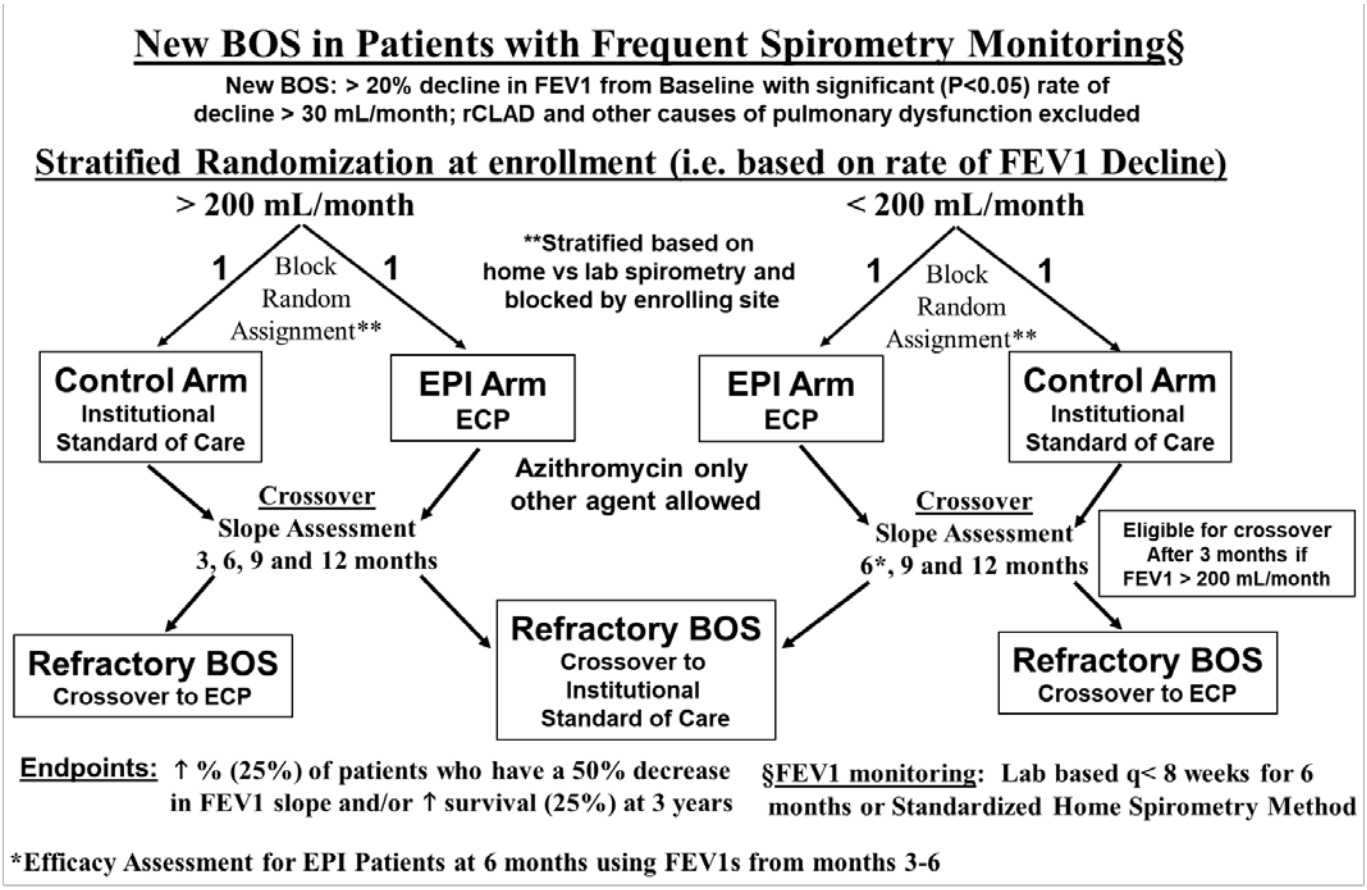
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RENATA ALBRECHT
12/22/2016

Appendix 3: Study Flow Diagram





APPENDIX 4 – ECP REGISTRY STUDY

SUBJECT IDENTIFICATION NUMBER _____

ECP PRE-PROCEDURE ASSESSMENT FORM

Please check (✔) the appropriate box(es) (Θ) and fill in the blank(s) as needed.

Date: : _____ Time: : _____	Procedure type: Θ Photo Machine Θ Cellex Θ UVAR cycles ___ Procedure consent signed on:_____	Procedure #	Time Out Completed Initials:_____ Time:_____
Patient Gender: ΘMale ΘFemale	Product #:	Location of procedure: Pheresis Center / Hospital Room Other:_____	

BASELINE ASSESSMENT Initials:

Patient Parameters	HT: _____ WT: _____lb/ _____kg HCT:_____ Date:_____ BMI:_____ Adjusted Body Wt:_____lb/_____kg Total Blood Volume: _____mL	Venous Access	Type: Θ Central Line Θ Port/IVAD Peripheral Other:_____ Location:_____ Date Placed:_____ Placement Verified by: Θ Electronic Record Θ Physician Dressing: Θ Dry/Intact Θ Changed CVC or IVAD abnormalities:_____ N/A Site: Θ No Drainage Θ No Redness
Neurologic	Θ Alert and Oriented x4 Θ Confused Θ Agitated Θ Sedated Θ Unresponsive Θ Slurred speech Θ New Memory Deficits Θ New arm/leg weakness	Edema	Θ Absent Θ Present: Θ 1+ Θ 2+ Θ 3+ Θ Location:_____
Respiratory	Θ Room Air Θ Nasal Cannula Θ O_2 _____L Θ Unlabored/Regular Θ SPO_2 _____% Θ Labored Θ Irregular Θ Mechanical Assist Θ Use of accessory muscles Θ Inability to talk Θ Wheezing (auscultation) Θ Audible stridor Other: :_____	Cardio Pulmonary	VS: BP _____ RR _____ Temp _____ Pulse _____ Θ Regular Θ Irregular Θ Denies any new symptoms Θ Difficulty breathing/ Θ New or change in SOB at rest or with exertion Θ Chest, arm, or jaw pain Θ Recent lightheadedness, near syncope or syncope
Skin	Θ Warm Θ Dry Θ Cool Θ Diaphoretic Color:_____	Activity	Θ Independent Θ Wheelchair Θ Bed rest Θ Walker Θ Cane
Injury or Fall	Θ None Θ Yes Description of Incident:_____	Medications Changes	Θ Medication list reviewed Θ Denies changes to current medication list Θ Changes Updated
Diagnostic Procedures	Performed in the last week or scheduled for upcoming week : Θ No Θ Yes Describe:_____	Signs of Infection	Θ Denies any of the following: Θ Fever Θ Chills Θ Night Sweats Θ Diarrhea Θ Persistent or Productive cough Θ Painful urination Other:_____
Pain	Θ Denies Θ Present Quality: Θ Dull Θ Aching Θ Stabbing Θ Burning Θ Throbbing Other:_____ Θ Frequency:_____ Θ Location:_____ Θ Intensity:_____ 0-10 scale greater than or equal to 4 requires comment	Signs of Bleeding	Θ Denies Θ Blood in stool, sputum or emesis Θ Nose Bleeds Θ Unexplained Bruising Θ Petechiae Θ Soft tissue hematomas Other:_____
		Hydration Status	Θ Denies any symptoms Θ Poor PO intake Θ Excessive Sweating Θ Postural symptoms

Physician or Nurse Practitioner contacted: Θ NO Θ YES /Name: _____

Approval given to begin procedure: Θ YES Θ NO Reason for contact/comments: _____