ECP REGISTRY

EXTRACORPOREAL PHOTOPHERESIS FOR THE MANAGEMENT OF PROGRESSIVE BROCHIOLITIS OBLITERANS SYNDROME IN MEDICARE-ELIGIBLE RECIPIENTS OF LUNG ALLOGRAFTS

MANUAL OF PROCEDURES

Version 1.0, for Protocol Version 4.0

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TABLE OF CONTENTS

1 INTRODUCTION 6

2 STAFF ROSTER 7

2.1 Senior Study Leadership 7

2.2 Clinical Coordinating Center (CCC) 8

2.3 Data Coordinating Center (DCC) 9

2.4 Clinical Centers 9

2.5 Data Safety Monitoring Board (DSMB) 10

3 TRAINING AND CERTIFICATION 11

3.1 Overview of Clinical Center Start-Up Requirements 11

3.2 General Requirements 12

3.3 Conflict-of-Interest Disclosures 12

3.4 Human Subject Research Training 12

3.5 Institutional Review Board (IRB) Approval 12

3.6 Certification for Medical Oversight of Study Patients 13

3.7 Certification for Extracorporeal Photopheresis Therapy 14

3.8 Certification for Pulmonary Function Outcomes Assessment 15

3.9 Delegation of Authority Log 15

3.10 Training and Authorization for Electronic CRF Submission 16

3.11 Site Initiation Visit 16

4 DRUGS AND DEVICES 17

4.1 Photosensitizing Drug – Methoxsalen 17

4.2 Extracorporeal Photopheresis Devices - UVAR and CELLEX 17

5 SCREENING AND ENROLLMENT 17

5.1 Patient Confidentiality (HIPAA) 17

5.2 Patient Identification 18

5.3 Screening Log 18

5.4 Inclusion Criteria 19

5.5 Exclusion Criteria 19

5.6 Screening Procedures Prior to Obtaining Informed Consent 20

5.7 Informed Consent 20

5.8 Eligibility Waiver Process 21

5.9 Pre-Enrollment Procedures After Informed Consent Has Been Obtained 21

5.10 Online Enrollment of Eligible Patients (see also DCC MOP Section 11) 22

5.11 Investigator Confirmation of Patient Eligibility 23

5.12 Documentation of Baseline Post-Enrollment Medical Status 23

6 MEDICAL MANAGEMENT OF STUDY PATIENTS 24

6.1 Routine Medical Care in Enrolled Participants 24

6.2 Maintenance Immunosuppressive Therapy 24

6.3 Management of Observation Arm Patients 24

7 ECP TREATMENTS 25

7.1 Timing of ECP Treatment Visits 26

7.2 Pre-Treatment Assessment on the Day of ECP Procedures 26

7.3 Performance of ECP Procedures 27

7.4 Documentation of ECP Treatment Visits 28

7.5 Pulmonary Function Testing 28

8 SUMMARY OF STUDY VISITS AND DATA SUBMISSION 28

8.1 Baseline – Required CRFs for All Enrollees (both treatment arms) 29

8.2 ECP Treatment Arm Patients (only) – Additional Required CRFs 29

8.3 Observation Arm Patients (only) – Additional Required CRFs 29

8.4 Supplementary CRFs to be Completed As Dictated by Clinical Circumstances 30

9.0 ADVERSE EVENT REPORTING 30

9.1 Definition of Adverse Event (AE) 30

9.2 Definition of Serious Adverse Event (SAE) 30

9.3 Pre-Existing Medical Conditions 31

9.4 General Reporting Requirements for AE and SAE 31
9.5 Adverse Event Worksheet and Serious Adverse Event CRF 32
9.6 Completion of Serious Adverse Event CRF 37
9.7 Review of SAE Categorization by CCC and DSMB 37
9.8 Other Reportable Events 37

10 DATA 38
10.1 Case Report Form Instructions 38
10.2 Data Clarifications 38
10.3 Source Documentation 39
10.4 DCC Reports to Clinical Centers 39
10.5 Data Confidentiality 40

11 SITE MONITORING 41
11.1 Site Monitoring Plan 41
11.2 Protocol Violations 41
11.3 Site Regulatory Binder 42
11.4 Patient Binder 42
11.5 Record Retention 42

12 SITE PAYMENT MECHANICS 42

13 POLICIES 42
13.1 Confidentiality 42
13.2 Clinical Center Staff Turnover 43
13.3 Study Website 43
13.4 MOP Maintenance 44

GLOSSARY OF ABBREVIATIONS

AE	Adverse event
ARO	Academic Research Organization
CAP	College of American Pathologists
CCC	Clinical Coordinating Center
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendment
CRF	Case report form
CT	Computed tomography
CV	Curriculum vita
DCC	Data Coordinating Center
DCQ	Data clarification query
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
ED	Emergency Department
EDC	Electronic data capture
ERL	Electronic Radiology Laboratory
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GI	Gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
HRPO	Human Research Protection Office
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
JCAHO	Joint Commission on the Accreditation of Healthcare Organizations
MOP	Manual of Procedures
OHRP	Office of Human Research Protection
PI	Principal Investigator
QOL	Quality of life
SAE	Serious adverse event
UP	Unanticipated Problem
UFH	Unfractionated heparin

1 INTRODUCTION

The primary aim of the Extracorporeal Photopheresis (ECP) Registry Study is to determine the efficacy and tolerability of ECP for the treatment of progressive bronchiolitis obliterans syndrome (BOS) after lung transplantation in a robust, multicenter patient cohort. In compliance with the Centers for Medicare and Medicaid Services' (CMS) Coverage with Evidence Development (CED) decision, the study will collect specified demographic, co-morbidity, treatment, and outcome data for Medicare beneficiaries who are treated with ECP for BOS. The study design is a prospective, single-arm cohort study including up to 15 participating centers. In total, about 182 patients are expected to be enrolled from lung transplant centers and other ECP providers with appropriate expertise, in order to reach 160 patients who actually receive ECP.

The ECP Registry was developed by investigators from the Departments of Pathology, Internal Medicine, and Mathematics at the Washington University School of Medicine in St. Louis, MO. Under the direction of Dr. George Despotis, Principal Investigator, the study is operationally coordinated by an Academic Research Organization (ARO) that is based within Washington University's Mallinckrodt Institute of Radiology. The conduct of the ECP Registry is sponsored by a research funding grant from Therakos, Inc. to Washington University. In addition, per its CED Program, CMS has agreed to provide reimbursement for the ECP procedures performed in study participants under a CMS Decision Memo (May 2, 2012, CAG-00324).

This Manual of Procedures (MOP) is designed to describe study flow to ensure that patient screening, enrollment, treatment, and follow-up are conducted in a structured, standardized manner. The MOP details how the data are observed, collected, and recorded. It specifies quality control procedures, methods for protecting participant safety and confidentiality of participant information, and an operational communication structure for the study. The MOP is a dynamic document that may be periodically amended to reflect Protocol changes and refinement of study procedures. The MOP is intended to serve both as a critical guide for proper study conduct and as a training manual for new investigators and coordinators.

2 STAFF ROSTER

2.1 Senior Study Leadership

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ARO Co-Director and DCC Director
Fred Prior, PhD
Research Associate Professor of Radiology
Mallinckrodt Institute of Radiology
Washington University School of Medicine
St. Louis, MO
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priorf@mir.wustl.edu

2.2 Clinical Coordinating Center (CCC)

The Clinical Coordinating Center (CCC), a component of the Washington University ARO, is the study's primary coordination and communication hub and will monitor and support the activities at the Clinical Centers. Most communication between the Clinical Centers and study leadership will flow through the CCC. Routine communications to the CCC can be directed to this address:

ECP Registry Clinical Coordinating Center
Mallinckrodt Institute of Radiology
Washington University School of Medicine
660 S. Euclid Ave., Box 8131
St. Louis, MO 63110
Phone: (314) 747-2372
Fax: (314) 747-1944

To directly contact CCC personnel who are best suited to handle a specific query, please use the contact information and responsibility areas of key CCC staff members noted below:

Director, Clinical Coordinating Center	Contact Information
Suresh Vedantham, MD vedanthams@mir.wustl.edu	Office Phone: (314) 362-2923 Cell Phone: (314) 283-8846
CCC Staff Members & Contact Information	**Responsibility Areas**
Mary Clare Derfler, RN, MSN Clinical Research Nurse Coordinator Phone: (314) 747-2372 derflerm@mir.wustl.edu	Study protocol questions Serious adverse event reporting Clinical issue with study patient Patient eligibility questions
Daniel Santacruz Special Project Administrator Phone: (314) 747-2498 santacruzd@mir.wustl.edu	Financial and contract issues General administrative issues
Kathy Taylor Clinical Research Coordinator Phone: (314) 747-1653 taylork@mir.wustl.edu	Clinical Center start-up Regulatory documents Data submission questions Updates to contact information

2.3 Data Coordinating Center (DCC)

The Data Coordinating Center (DCC), a component of the Washington University ARO, is based at the Electronic Radiology Laboratory (ERL) within the Mallinckrodt Institute of Radiology. The DCC will centrally coordinate the study's data management. Contact information and roles for key DCC personnel are provided here:

Director, Data Coordinating Center	Contact Information
Fred Prior, PhD	Phone: (314) 747-0331 priorf@mir.wustl.edu
DCC Team Members	**Responsibility Areas**
Paul Commean, BEE Project Manager/Software Developer Phone: (314) 362-8497 commeanp@mir.wustl.edu	Oversight of DCC staff efforts Website Design & Maintenance Database Manager
David Maffitt, MS, MS Software Developer Phone: (314) 362-1476 maffittd@mir.wustl.edu	Database Design & Implementation Website Design & Maintenance Oversee IT Troubleshooting Username/Password Manager
Joan Moulton, BS Technical Coordinator Phone: (314) 362-7185 moultonj@mir.wustl.edu	Help Desk Manager Case Report Form (CRF) Questions CRF Verification Questions
Mary Wolfsberger, AAS Technical Coordinator Phone: (314) 362-7194 wolfsbergerm@mir.wustl.edu	Help Desk Manager CRF Questions CRF Verification Questions

2.4 Clinical Centers

See the ECP study website (http://ecpregistry.wustl.edu) for an updated list of Clinical Centers.

2.5 Data Safety Monitoring Board (DSMB)

The ECP Registry is monitored by a DSMB that is independent of the study investigators. A description of the DSMB is contained in its Charter (available by request). ECP Registry study site investigators and site research staff are not permitted to directly discuss the study with any of the DSMB members. ECP Registry leadership and their staff will avoid communication with the DSMB except for situations specified in the DSMB Charter and CCC standard operating procedures for adverse event review. Communications for the DSMB should be directed to Dr. Suresh Vedantham or Dan Santacruz at the CCC. The members of the DSMB are listed below:

Chair, DSMB
Jeffrey Winters, MD
Professor of Laboratory Medicine and Pathology
Mayo Clinic College of Medicine
Rochester, MN

DSMB Members
Edward Garrity, Jr., MD
Professor of Medicine
University of Chicago
Chicago, IL

Phillip Miller, PhD
Professor of Biostatistics
Washington University
St. Louis, MO

3 TRAINING AND CERTIFICATION

3.1 Overview of Clinical Center Start-Up Requirements

The CCC will ensure that all ECP Registry Clinical Centers have met the following important start-up requirements before approving them to begin enrolling patients in the study:

REQUIREMENT	RESPONSIBLE	SECTION
Signed, dated CV – Site PI, co-Investigators, coordinator	CCC	3.2
Medical License - Site PI and Co-Investigators	CCC	3.2
IRB Roster or IRB Assurance Letter and FWA Letter	CCC	3.2
Fully Executed Subaward	CCC	3.2
Conflict-of-Interest Disclosure – Site PI, Co-Investigators	Clinical Center	3.3
Human Subjects Research Training Certificate	On File At Site	3.4
IRB Approval Letter for Study Protocol	CCC	3.5
IRB-approved, Stamped Informed Consent Form (ICF)	CCC	3.5
HIPAA Authorization – if not included in ICF	CCC	3.5
Partial Waiver of HIPAA Authorization	CCC	3.5
CV, Medical License, Board Certificate – Transplant Pulmonologist	CCC	3.6
CV, Medical License, Board Certificate – Transfusion Medicine Specialist	CCC	3.6
JCAHO, CAP, and CLIA Certifications	CCC	3.6
Lab Normal Ranges, Director's Medical License and CV	CCC	3.6
Receive Medical Oversight Certification Letter	**From CCC**	**3.6**
ECP Co-Investigator – CV, Medical License, Board Certificate	CCC	3.7
ECP Co-Investigator – ECP Experience Information	CCC	3.7
Pheresis Center – ECP Experience Information	CCC	3.7
Pheresis Center – Plan for Obtaining Pre-ECP CBCs	CCC	3.7
Pheresis Center – Plan for Emergencies, Acute Response Team	CCC	3.7
Availability of UVAR or CELLEX for ECP	CCC	3.7
SOPs – Infections, Catheters, Patient Assessment, Photosensitivity	CCC	3.7
Receive Photopheresis Therapy Certification Letter	**From CCC**	**3.7**
PFT Lab – Availability of Certified Technologists	CCC	3.8
PFT Lab – Attestation of Adherence to ATS Guidelines	CCC	3.8
PFT Lab – Lab Director's CV and Medical License	CCC	3.8
Complete Training Module on Data Entry, with Attestation	DCC	3.9
Delegation of Authority Log	CCC	3.10
Successful Completion of Site Initiation Visit by CCC	CCC	3.11
Receive Site Initiation Approval Letter	**From CCC**	**3.11**

After completion of all requirements above, the CCC will issue a ***Site Initiation Approval Letter***, signed by Dr. Despotis. Sites may not enroll patients until they receive this letter.

3.2 General Requirements

Each Clinical Center should field a multidisciplinary research team that includes: 1) a physician co-investigator experienced in managing lung transplant patients with BOS; 2) a physician co-investigator experienced with the use of ECP; and 3) a research coordinator. Any deviation from this requirement must be approved by Dr. Despotis. Signed, dated curriculum vitae (CV) and medical licenses for each co-investigator must be submitted to the CCC. The CCC must also have a fully executed subaward between Washington University and the Clinical Center. Copies of these documents, the site's Institutional Review Board (IRB) Roster or IRB Assurance Letter, and its Federal Wide Assurance Letter should be kept in the Site Regulatory Binder.

3.3 Conflict-of-Interest Disclosures

Each Clinical Center must have in place a policy and process for identifying and resolving conflicts-of-interest that is compliant with current federal regulations. Each investigator must maintain an updated conflict-of-interest disclosure with the Clinical Center's internal review board. If a potential conflict is identified, the Clinical Center must notify Washington University of the existence of the potential conflict, its nature, and how it was resolved.

3.4 Human Subject Research Training

Each Clinical Center is responsible for ensuring that each individual involved in the conduct of the ECP Registry at the site has undergone training in the appropriate conduct of human subject research. The human subject training certificates of the site PI and all other engaged personnel (co-investigators, other physicians that will interact with subjects for research purposes, coordinators, etc.) should be placed in the Site Regulatory Binder.

3.5 Institutional Review Board (IRB) Approval

Prior to the initiation of a Clinical Center, the ECP Registry Protocol, Informed Consent Form (ICF), and HIPAA Authorization (if separate from the ICF and if not already routinely obtained by the Clinical Center) must be reviewed and approved by the Center's local IRB, and must subsequently undergo annual IRB review with approval of any amendments. IRB submission documentation, all correspondence with the IRB about the study, contingency letters, and all approval letters should be maintained at the Clinical Center in the Site Regulatory Binder. A copy of all IRB approval letters, IRB-approved ICFs, and HIPAA Authorizations must be provided to the CCC. To keep all sites working concurrently on the same Protocol version, IRB

approval on all amendments should be obtained within 60 days of their posting. For Protocol amendments, after verification that IRB approval for the new version has been obtained, the CCC will send the site a Site Conversion Approval Letter that approves the site to begin working on the new Protocol version. The CCC will notify the DCC, and the DCC will convert the site to the new version in the electronic database, if this is needed.

For initial IRB Protocol approval and for amendments where there are significant changes to the informed consent language, each Clinical Center must submit its informed consent form (ICF) draft to the CCC for review and approval before submitting it for local IRB review. The CCC will make every effort to provide review comments on the ICF to the site within 7 days. After a Clinical Center's ICF is approved by the CCC, it may be submitted to the local IRB. After IRB approval is obtained, the IRB-approved, stamped ICF must be submitted to the CCC. Sites will not be initiated until the ICF is approved by both the CCC and the local IRB.

3.6 Certification for Medical Oversight of Study Patients

To ensure patient safety, the ability of each Clinical Center to provide appropriate medical oversight of study participants must be certified by the CCC prior to site initiation. This process involves submission of the following materials to the CCC for review by study leadership:

Co-Investigator Credentials - The current signed, dated curriculum vitae, medical licenses, and board certificates of the Clinical Center's transplant pulmonologist and transfusion medicine specialist should be submitted to the CCC. Either person may be the site PI or a designee, but both must be appropriately trained physicians who are experienced with either the management of post-lung transplantation BOS or with the performance and/or oversight of pheresis procedures (preferably ECP), and who have active medical licenses in the state where the Clinical Center resides. These individuals are expected to ensure quality control of the medical management of enrolled patients during the study.

Hospital Accreditation and Laboratory Certifications - Proof of hospital accreditation by the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) and the clinical laboratory's Clinical Laboratory Improvement Amendment (CLIA) and College of American Pathologists (CAP) certifications should be provided to the CCC. A list of normal Lab values and the Lab Director's CV and medical license should be kept in the Site Regulatory Binder.

Review Process: When all of the above items have been received by the CCC, the study leadership will review them and provide a recommendation (approve, reject, or request more

information) to the CCC. CCC staff will communicate this decision, and any request for additional documentation, to the Clinical Center. Once the Clinical Center is approved by the study leadership, the CCC will provide a ***Medical Oversight Certification Letter*** to the Clinical Center. Clinical Centers may not be initiated until they have received this certification. Questions concerning medical oversight certification, and appeals on decisions, may be directed to Dr. George Despotis, ECP Registry Principal Investigator.

3.7 Certification for Extracorporeal Photopheresis Therapy

To ensure that ECP is delivered to study patients in a manner compatible with current quality clinical practice, the ECP procedures must be supervised by qualified physicians with appropriate experience, in Pheresis Centers that have the requisite capabilities to provide quality care. The designated ECP co-investigator (who may be the site PI or a designee) and the Pheresis Center where ECP will be performed must be certified by the CCC prior to site activation. This process involves submission of the following materials to the CCC:

ECP Co-Investigator Credentials – All ECP procedures in study patients must have oversight by an appropriately trained, board-certified physician with an active medical license in the state where the Clinical Center resides. The current signed, dated CVs, medical licenses, and board certificates of all ECP co-investigators should be submitted to the CCC, along with a brief statement of prior experience that includes the numbers of pheresis and ECP procedures performed for any indication, and for BOS in post-lung transplant patients.

ECP Device Availability: Prior to initiation, each Clinical Center must inform the CCC if it possesses a Therakos UVAR and/or Therakos CELLEX extracorporeal photopheresis unit.

Pheresis Center Capabilities and Experience: Prior to initiation, each Clinical Center must provide to the CCC a brief statement of its experience with ECP that includes, at a minimum: a) the number of years performing ECP for any indication; b) the number of ECP procedures performed within the past 12 months for any indication; and c) the number of ECP procedures performed within the past 12 months for post-lung transplant BOS. The Clinical Center must provide to the CCC the institutional policy documents that detail standard operating procedures of the Pheresis Center with respect to ensuring the following elements of safe peri-ECP care: 1) prevention of infection; 2) safe use of central venous catheters and prevention of air embolism; 3) pre-ECP patient assessment; and 4) patient protection against photosensitivity injuries. Any exceptions to these requirements must be approved by Dr. Despotis.

Review Process: When the above items have been received by the CCC, the study leadership will review them and provide a recommendation (approve, reject, or request more information) to the CCC. CCC staff will communicate this decision, and any request for additional information, to the Clinical Center. Once the Clinical Center is approved, the CCC will provide a ***Photopheresis Therapy Certification Letter*** to the Clinical Center. Clinical Centers may not be initiated until they receive this certification. Please direct any questions about photopheresis therapy certification, or appeals on decisions, to Dr. George Despotis, Principal Investigator.

3.8 Certification for Pulmonary Function Outcomes Assessment

To ensure the study's integrity in terms of its primary outcome assessments, pulmonary function tests in ECP Registry enrollees must be performed by Registered Respiratory Therapists (RRT), Certified Pulmonary Function (CPF) technologists, or Registered Pulmonary Function (RPF) Technologists with adherence to guidelines of the American Throracic Society (ATS). Prior to site initiation, each Clinical Center should identify to the CCC the pulmonary function laboratory in which study patients will be predominantly evaluated, and provide to the CCC the lab Director's CV and medical license and the site PI's attestation that the testing in study patients will be performed by RRT, CPF, and /or RPF technologists adhering to ATS guidelines.

Review Process: The study leadership will review the above information and provide a recommendation (approve, reject, or request more information) to the CCC. CCC staff will communicate this decision, and any request for additional information or documentation, to the Clinical Center. Once the Clinical Center is approved, the CCC will provide a ***Pulmonary Outcomes Certification Letter*** to the Clinical Center. Clinical Centers may not be initiated until they receive this certification. Questions concerning pulmonary outcomes certification, and appeals on decisions, may be directed to Dr. George Despotis, Principal Investigator.

3.9 Delegation of Authority Log

Prior to site initiation, the Clinical Center must submit a Delegation of Authority Log to the CCC. The Delegation of Authority Log is the study personnel responsibility list. This Log includes the name, signature, initials and PI-delegated study-related tasks of all individuals involved in the trial. Once completed and signed by the PI, the Log should be e-mailed or faxed (314-747-1944) to the CCC. The Log should later be updated to reflect study personnel changes, as needed. After the Log is updated, the site PI should re-sign and re-date the form.

3.10 Training and Authorization for Electronic CRF Submission

Prior to site activation, each investigator, coordinator, and designated personnel must undergo training on the use of the Electronic Data Capture (EDC) system for web-based data entry. Before enrolling a patient or entering data on any case report forms (CRFs) via EDC, each user must complete the relevant components of the training module for the EDC system on the study website. The details of this process are described in the DCC's EDC Operating Manual. The training modules are also available in the "Investigator Resources" section of the ECP Registry study website at http://ecpregistry.wustl.edu.

To obtain username and password to the EDC system, the site's Delegation of Authority Log must state that the user may enter data (enter subject eligibility information and/or electronic CRF data) into the EDC system. The DCC will then provide each properly delegated site user with log-in and password information to access the EDC system.

Users should complete the online training along with the instructional training modules as soon as possible after receiving their log-in information. The training modules are located in the username/password protected "Site Resources" section of the ECP Registry website under the menu item "Investigator Resources". Following review of the training modules, the user must sign the attestation form attesting that he/she has completed the online training, and submit a copy of the form to the CCC. The original form should be kept in the Site Regulatory Binder.

3.11 Site Initiation Visit

Once the CCC has confirmed that all other requirements for study start-up have been met, a CCC staff member and often Dr. Despotis will visit the Clinical Center at a mutually convenient time. At this visit, the CCC team member(s) will provide any additional training needed to ensure an adequate understanding of the study Protocol, processes, and expectations. The CCC team will meet with the site PI, study coordinator, study co-investigators as available, and will visit the Pheresis Center and areas where research records are maintained. After this visit, a summary report will be developed and a ***Site Initiation Activation Letter*** sent to the site PI if all start-up requirements have been met. This Letter, which will be signed by the Principal Investigator, Dr. George Despotis, authorizes the site to start enrolling patients in the study.

4 DRUGS AND DEVICES

4.1 Photosensitizing Drug – Methoxsalen

Methoxsalen is a photosensitizing drug that is used for extracorporeal conditioning of lymphocytes extracted from the vasculature, prior to UVA irradiation and reinfusion of these cells. Methoxsalen has been approved by the FDA for the treatment of cutaneous T-cell lymphoma, and is used off-label for BOS in this study. The FDA has provided an IND Waiver to Dr. George Despotis, Principal Investigator, for the use of methoxsalen (UVADEX) in the ECP Registry Study. Clinical Centers are expected to use their own supply of injectable methoxsalen and to store, reconstitute, dilute, and dispense the drug per the Clinical Center's standard practice which should parallel the instructions in the UVADEXpackage insert. Oral administration of methoxsalen or related compounds may not be used in study participants.

4.2 Extracorporeal Photopheresis Devices - UVAR and CELLEX

ECP 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 these systems (e.g. prerequisite criteria for minimum hematocrit ≥ 28% before each procedure). The FDA has informed Dr. George Despotis that an IDE is not needed for this study.

5 SCREENING AND ENROLLMENT

5.1 Patient Confidentiality (HIPAA)

All ECP Registry study personnel must adhere strictly to HIPAA guidelines. At each Clinical Center, ECP Registry participants should be informed what safeguards are being taken to protect the privacy of their health information. Study participants will be identified by a study-specific Participant Identification (ID) Number only. Information provided by the ARO and Washington University investigators to Therakos (to keep them abreast of overall study progress and specific categories of serious adverse events) will be de-identified.

A signed HIPAA Authorization Form must be obtained from each participant unless this authorization is already obtained from the ICF or other document. The HIPAA Authorization Form describes patient and data confidentiality associated with the study. A blank copy should be kept in the Site Regulatory Binder, and the signed HIPAA Authorization Form for each individual patient should be kept in the Patient Binder along with the signed ICF.

5.2 Patient Identification

Each site PI should place high priority upon pro-actively crafting and internally communicating a site-specific plan for identifying potential study patients. Incorporation of ECP Registry screening into departmental BOS treatment algorithms (or, achievement of department-wide study awareness at a minimum) should be actively sought, when possible.

At the participating Clinical Centers, potential participants may be identified by study staff, physician investigators and co-investigators, other physicians, and thorough 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.

A successful enrollment strategy will minimize the study's burden upon clinical personnel who are not part of the research team. In general, such personnel may be asked to identify potential participants, but the time-consuming burden of establishing patient eligibility for the study should be shouldered by the research team. Trying to confer additional responsibilities upon clinical personnel will only deter them from notifying the research team about the patient. Use of patient recruitment strategies and materials are subject to the policies and preferences of the local IRB.

Resources: Printed ECP Registry Study advertising materials and protocol cards containing the study eligibility criteria will be provided to each Clinical Center upon site initiation. To re-order these materials, please contact the CCC.

5.3 Screening Log

A record of all patients who are screened for the ECP Registry and meet the study inclusion criteria but who are not enrolled (either due to meeting one or more study exclusion criteria, or due to unwillingness to provide informed consent) should be maintained in a Screening Log. Acceptable entries must document patient status with respect to all exclusion criteria that do not require additional testing to evaluate, and his/her willingness to participate. The paper Screening Log should be e-mailed monthly to the CCC. A copy of each monthly Screening Log should also be kept in the Site Regulatory Binder. No patient identifiers should be provided on the Screening Log. Screened patients that meet the study inclusion criteria but who are not subsequently enrolled should be identified by a sequential Screening Identification Number consisting of the letter "S" followed by a 3-digit number (i.e. S001, S002, S003, etc.).

5.4 Inclusion Criteria

All patients must meet *all* of the following participant Inclusion Criteria in order to participate:

1. Adult age (at least 18 years old)
2. Medicare-eligible status
3. Lung transplant recipient (combined organ transplant recipients, e.g. heart-lung or liver-lung recipients, are eligible).
4. Strong clinical suspicion for progressive 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).
5. At minimum five recorded FEV_1 measurements obtained at intervals of at least one week apart, over the 6 months preceding study enrollment.

5.5 Exclusion Criteria

Patients meeting *any one* of these Exclusion Criteria are not eligible for the study:

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, or 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 1 week 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).

5.6 Screening Procedures Prior to Obtaining Informed Consent

When a potential participant becomes known to the site's research team, the investigator and/or an appropriately designated staff member should screen the medical history, laboratory studies, and past pulmonary function tests to determine if he/she must clearly be excluded from the study, either by a) clear failure to meet all study inclusion criteria; or b) clear fulfillment of one or more study exclusion criteria. Although most exclusions can be assessed prior to approaching the patient, it is important to remember that any additional testing to assess patient eligibility may not be performed until informed consent is obtained and documented.

Once it is determined that the patient meets all inclusion criteria and that he/she does not meet any of the exclusion criteria, and the patient's physician approves his/her study participation, then the research team may proceed with the informed consent process described below.

Once it becomes clear that a patient must be excluded, the research team should complete a Screening Log entry. Because description of the population characteristics of non-included patients is important to assess the study's external validity, all listed eligibility criteria that do not require additional testing to evaluate should be documented in the Screening Log. A patient's decision to decline participation should be also recorded on the Screening Log, if applicable.

5.7 Informed Consent

As required by CFR 45 Part 46.117, a signed informed consent form (ICF) must be obtained prior to enrollment or the performance of protocol-driven screening tests or procedures for all patients in the ECP Registry. Permission should be obtained from the potential participant's physician before initiating an informed consent discussion. The study investigator or coordinator should initially ask the potential participant open-ended questions to assess his/her level of comprehension. Cognitively impaired persons should not be offered participation in the study. The study investigator or coordinator should discuss with the patient the purpose of the study, the duration of participation, study procedures, visit obligations, and potential risks, benefits, and alternatives to participation. The research team member should allow ample time for the prospective participant to carefully read the ICF and have any questions answered. The ICF should be provided to the patient in a certified translation of his/her native language. The informed consent process must be conducted in a non-coercive manner. Every potential participant should know that he/she is not obligated to participate, that there is no penalty for non-participation, and that his/her medical care will not be compromised if he/she chooses not to participate or later withdraws. All patients should be informed that a) 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; and that b) to limit the use of ECP to patients 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.

The ICF should be written in lay language rather than scientific or legal terminology. All ICF forms for the ECP Registry must contain all elements required by 45 CFR 46.116. Informed consent regulations are administered by the Office of Human Research Protections (OHRP); their website (http://www.hhs.gov/ohrp/humansubjects/guidance/ictips.htm) provides tips to guide investigators in developing informed consent documents.

If there are updates to the study Protocol or new medical information is identified that may impact a patient's decision to participate, study participants may need to be re-consented during the study. If a new informed consent is required, the process is repeated; however, the old informed consent is kept as a source document of the original informed consent process.

The site principal investigator or designee and the study participant must each sign and date the ICF. The study participant should be provided with a copy of the signed and dated ICF. The original signed and dated ICF should be placed in the Patient Binder at the site. The informed consent discussion should be briefly documented in the patient's medical record.

5.8 Eligibility Waiver Process

Eligibility waivers will not be granted except in the most unusual of circumstances, but may be submitted to Dr. George Despotis, Principal Investigator, for consideration.

5.9 Pre-Enrollment Procedures After Informed Consent Has Been Obtained

A physical examination, vital signs, urine or blood pregnancy test in women of childbearing potential, and pulmonary function testing must be obtained within 1 week prior to enrollment. Once informed consent is obtained, site personnel will collect the following source information that will be necessary to enroll the patient on the ECP website: a) all available pulmonary function test reports from the preceding 6 months, of which one FEV-1 value must have been obtained within the preceding 7 days; b) Operative Report of the Transplant procedure; and c) History and Physical or Consultation note that documents the physician's determination that there is strong clinical suspicion for progressive BOS.

5.10 Online Enrollment of Eligible Patients (see also DCC MOP Section 11)

To enroll a patient, go to http://ecpregistry.wustl.edu and follow the steps below:

1. Click on Site Resource Login (button) or Login (main menu) to access the study website.

2. Enter Username and Password on the Login page (Please call the-Helpdesk at (314) 362-7185 or (314) 362-7194 if you encounter problems with your username or password).

3. Click on "Check Enrollment/Arm Eligibility". When this is done, the "Enrollment Assessment and Study Eligibility" form will appear.

4. Confirm the presence of all the Inclusion Criteria and the absence of all of the Exclusion Criteria by answering Yes to the Inclusion Criteria and No to the Exclusion Criteria. **To avoid enrolling non-eligible subjects, re-confirm any questionable items before submitting.**

5. Enter all available pre-bronchodilator FEV-1 and FVC values for the preceding 6 months, of which one FEV-1 value must have been obtained within the preceding 7 days. Enter the FEV-1s from the oldest date at the top to the newest date at the bottom, up to a total of 15 values. A minimum of five FEV-1 values post-transplant must be entered from the last 6 months, separated from each other by at least one week. **It is imperative that all FEV-1 values and PFT testing dates are entered correctly and that they correspond exactly to the information on the source documents (PFT exam reports) – please check that this is the case before clicking "Determine Enrollment and Study Arm Eligibility".**

6. Enter the date the patient signed the IRB-approved Informed Consent Form, and the Informed Consent Form version date.

7. Click Determine Enrollment and Study Arm Eligibility again.

Once patient eligibility is confirmed by the online web module, the system will calculate the rate of FEV-1 decline based on the information entered. At this point, the patient will be assigned a unique Participant ID Number, and will also be electronically assigned to either the **ECP Treatment Arm** or to the **Observation Arm** of the study based on the information entered, per the criteria described in ECP Registry Protocol Section 3.6. The information that was entered into the "Enrollment Assessment and Study Arm Eligibility" form will automatically populate into the Confirmation of Eligibility CRF, and will be saved in the EDC system. Irrespective of

treatment arm assignment, at this point the patient is considered enrolled in the ECP Registry.

Additional resources describing the enrollment process can be found under the Investigator Resources main menu item in the "Site Resources" part of the website (http://ecpregistry.wustl.edu).

5.11 Investigator Confirmation of Patient Eligibility

Ideally within 24 hours and no later than 3 business days (Monday-Friday) after the time of enrollment (defined as the time when the Participant ID Number is generated by the online system), a properly designated site investigator (i.e. the site PI or a delegated physician co-investigator) must sign and date a printed copy of the Confirmation of Eligibility CRF. Once this is done, the signed and dated Confirmation of Eligibility CRF must then be uploaded into the EDC system along with the required source documentation (see MOP Section 5.9). The DCC will then verify the CRF against the source documents.

Once verified by the DCC, the participant visit schedule and, for appropriate CRFs (depending on treatment arm assignment), will then populate within that patient's entry in the EDC system.

Patients may not undergo ECP or other study-related invasive procedures (e.g. central venous catheter placement) until after the investigator (the site PI or a delegated physician co-investigator) has attested to the participant's eligibility by signing and dating the Confirmation of Eligibility CRF (electronically or by written signature), and that CRF has been verified by the Data Coordinating Center. If this process needs to be expedited because of patient scheduling logistics, please contact the help desk or CCC coordinator.

5.12 Documentation of Baseline Post-Enrollment Medical Status

Once the patient is enrolled, his/her medical history, post-transplant baseline FEV_1 (as defined by the standard ISHLT definition), previous and current medications, physical examination, vital signs, and resting oxygen saturation should be documented in the medical record and recorded on the Demographics/Medical History CRF. Concomitant medical therapy, including prednisone and any other immunosuppressive, anticoagulant, or antiplatelet drug that is being used, should be recorded on the Baseline Therapy CRF. For details on how to complete these two CRFs, please refer to DCC MOP Sections 12.2 and 12.3. Site personnel should also collect all FEV-1 values that have been obtained in the patient since transplantation, and maintain the corresponding pulmonary function testing reports in the Patient Binder at the site.

6 MEDICAL MANAGEMENT OF STUDY PATIENTS

6.1 Routine Medical Care in Enrolled Participants

After study enrollment into either treatment arm, infection prophylaxis and other physician-prescribed care should be continued per standard medical practice at the site. Women of childbearing potential who are in the ECP Treatment Arm will be instructed to use an effective contraception method during their time in the study, and will be instructed to notify the research team immediately if pregnancy occurs or if the contraceptive method fails in any manner.

6.2 Maintenance Immunosuppressive Therapy

It is expected that most patients will be treated with triple-drug immunosuppression consisting of a calcineurin inhibitor (tacrolimus or cyclosporine A), a cell cycle inhibitor (mycophenolate mofetil or azathioprine), and prednisone. However, this research protocol does not require the use of a specific maintenance immunosuppressive regimen, or specific alterations in the immunosuppressive regimen to manage BOS, and sites may choose specific regimens for patient-specific reasons. Similarly, infection prophylaxis protocols vary among centers, and participants may be treated according to local standard clinical practice. Patients may also continue to receive their physician-prescribed treatments for other conditions.

As noted above, baseline concomitant medical therapy will be recorded in ECP Registry enrollees on the Baseline Therapy CRF. If medical therapy changes (e.g. initiation or cessation of any immunosuppressive, anticoagulant, or antiplatelet drug or change in prednisone dose), this should be documented using the Change in Therapy CRF in the EDC system.

6.3 Management of Observation Arm Patients

Observation Arm patients should be seen and managed per routine physician-directed clinical practice. If progressive BOS is still suspected, the site investigator may obtain up to 4 additional FEV-1 measurements at intervals of no less than 7 days. The results of these additional tests should be entered in the EDC system on the Pulmonary Evaluation CRF. These values will automatically populate (along with the originally entered initial FEV-1 values) on the Observation Pulmonary Evaluation Log once verified by the DCC. If desired by the investigator, the patient's eligibility to receive ECP treatment may be re-checked in the EDC system by selecting "Check ECP Treatment Eligibility" on the Observation Pulmonary Evaluation Log.

The patient can be enrolled subsequently into the ECP Treatment Arm if the rate and statistical significance of FEV_1 decline now meet the study's criteria and the site research team confirms online that the patient has not developed a new contraindication to the use of ECP therapy by answering this question on the Crossover Safety Check CRF. 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 Arm based on his/her clinical judgment ("clinical override"), provided that the rate of FEV_1 decline meets the study's cut-off threshold (-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. The Crossover Safety Check CRF should be signed by a site investigator, ideally within 24 hours but at most within 3 days.

Patients who are crossing over from the Observation Arm to the ECP Treatment Arm may not undergo ECP or other study-related invasive procedures (e.g. central venous catheter placement) until after the investigator (i.e. site PI or a physician co-investigator) has attested to the subject's suitability for ECP by signing and dating the Crossover Safety Check CRF, and the form has been verified by the Data Coordinating Center. If this process needs to be expedited because of patient scheduling logistics, please contact the help desk or CCC coordinator.

Patients who continue in the Observation Arm but who experience a decline in pulmonary function may be re-evaluated for potential crossover into the ECP Treatment Arm after a minimum of 2 months has passed, 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 Arm will be followed for 1 year after the initiation of ECP.

7 ECP TREATMENTS

If the patient is assigned to the ECP Treatment Arm, preparations for ECP may be made once the investigator-signed Confirmation of Eligibility CRF (or Crossover Safety Check CRF, if applicable) has been verified by the DCC. The use of peripheral venous access for ECP is strongly encouraged to reduce the occurrence of central venous catheter-related infections, but the site may determine which form of venous access will be utilized for study patients.

7.1 Timing of ECP Treatment Visits

Per ECP Registry Protocol Section 4.2, patients 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 (preferably twice weekly);
- 8 to 10 treatments in the next 60 days (months 2 and 3); and
- 6 treatments in the next 90 days (months 4 through 6) (2 treatments per month).

Please note that an FEV-1 value must be obtained on, or within 7 days prior to, the day of the first ECP treatment even if an FEV-1 value was already obtained within 7 days prior to study enrollment (please see Protocol Section 3.5 and Protocol Section 5.3 for the two separate requirements). In fact, testing < 48 hours before the first ECP treatment is strongly preferred.

Each treatment should be given on a separate day. The 24 Treatment Visits will be numbered sequentially from ECP Treatment 1 through ECP Treatment 24 within the online EDC system. Site personnel may modify the ECP treatment visit schedule as dictated by ongoing medical circumstances (e.g. recent hospitalization for an acute medical illness), or if the pre-treatment assessment on the day of a planned procedure suggests that the patient's condition is not suitable for ECP. However, the reason for cancellation or postponement of treatment should be documented in the medical record and in a Note to File in the Patient Binder at the site. Beyond this, site personnel should try to maintain fidelity to the above schedule of ECP treatment visits. Patients should be routinely reminded of the importance of receiving treatment as planned.

7.2 Pre-Treatment Assessment on the Day of ECP Procedures

At each ECP treatment session, prior to initiating ECP, patients must be clinically assessed by the institution's clinical personnel to ensure that they are in suitable condition to undergo ECP that day. This should include an assessment of vital signs (including blood pressure, heart rate, and respiratory rate), weight, oxygen saturation, and the other elements in the ECP Pre-Procedure Assessment Form (see Protocol Appendix 3). A CBC with differential must also be obtained prior to, and on the same day as, each ECP treatment (except for patients who undergo ECP treatment one day after the last ECP treatment and who have a CBC from the previous day). The ECP Pre-Procedure Assessment Form should be completed before each treatment session and filed in the Patient 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, per the institution's standard practice) should assess the patient to determine if further clinical or laboratory investigations are required, and ultimately determine if ECP is safe to perform on that day. Per Protocol, ECP should not be performed if the hematocrit is less than 28% or if there is clinical concern for hypovolemia or any other medical condition that places the patient at increased risk for a complication; and in fact, we strongly recommend that ECP not be performed with a hematocrit < 30%. Alternative policies for pre-procedure ECP assessment that are similar to the ECP Pre-Procedure Assessment Form in ECP Registry Protocol Appendix 3 may be followed, if reviewed and approved by Dr. Despotis.

7.3 Performance of ECP Procedures

ECP should be performed per the site's standard practice, with consideration of the following guidance to promote safe treatment. If a central venous catheter or implantable port is used, local best practices to assure safe placement should be followed, with sterile technique, either ultrasound or fluoroscopic guidance for venipuncture, and subsequent physician verification that the catheter is in proper position. Central venous catheters should be managed with extreme care to minimize the risk of infection and air embolism. The use of heparin should be avoided in patients who are at risk for bleeding complications or who have an allergy to heparin; in this case, citrate can be considered as an alternative anticoagulant using the institution's local protocol if this is acceptable to the local physician. Attention should be given to preventing citrate toxicity, with administration of calcium gluconate solution as needed, per local standard practice. After ECP, patients should be monitored for complications per local standard practice and should be provided with explicit instructions to avoid sun exposure (including sunlight through windows) for 24-48 hours after each ECP treatment (ideally). Patients should be instructed to wear hats, protective clothing, sunscreen (SPF 15 or higher), and UV-resistant wraparound sunglasses if exposure will occur within the first 24-48 hours after ECP treatment.

In general, the typical therapeutic process target for ECP using the UVAR device (small bowl) is 5-6 cycles, while 3 cycles are generally considered therapeutic when using the large bowl with the UVAR device. The typical therapeutic process target for ECP using the CELLEX device is 1500 mL whole blood. If these targets are not reached, the reason(s) why should be recorded on the ECP Treatment CRF. The attainment of markedly subtherapeutic targets (e.g. less than 3 cycles with UVAR large bowl, less than 4 cycles with UVAR small bowl, or less than 1000 mL with CELLEX) without a strong clinical justification for reduced processing will be evaluated as suspected protocol violation.

7.4 Documentation of ECP Treatment Visits

An ECP Treatment Visit CRF should be completed after each ECP treatment visit to document the patient's clinical status on the day of ECP, to record treatment parameters, and to document if treatment was completed as planned and uneventfully.

During the pre-treatment assessments, the patient's medications should be reviewed. If any immunosuppressive, anticoagulant, or antiplatelet medications have been started or discontinued, this should be recorded on the Change in Therapy CRF. If changes in prednisone dosing have occurred, this should be recorded on the Change in Therapy CRF.

At each visit, patients should be queried for any untoward medical occurrences (including new symptoms or signs) that have occurred since the preceding visit. Any occurrences that meet the definition of an adverse event should be assessed for reportability using the Adverse Event Worksheet. If the event meets the definition of a reportable Serious Adverse Event, the entire Serious Adverse Event CRF must be completed and submitted to the DCC per Protocol.

7.5 Pulmonary Function Testing

Spirometry should be measured by certified and trained technicians per American Thoracic Society (ATS) guidelines, per ECP Registry Protocol Section 5.3. The study will capture FEV_1 data through spirometry during the course of ECP therapy in accordance with the following schedule: Days 0, 30, 60, 90, 120,150, 180, 240, 300 and 365 (note - Day 0 refers to the day of, or within one week prior to, the first ECP treatment; that said, obtaining an FEV1 value within 48 hours prior to the first ECP treatment is strongly preferred). Spirometry from Day 0 through Day 120 may be performed within $\pm$7 days to accommodate patient or provider scheduling needs, and spirometry from Day 150 through Day 365 may be performed within $\pm$14 days.

8 SUMMARY OF STUDY VISITS AND DATA SUBMISSION

This section contains a basic description of the data that will be submitted for each study visit. Please refer to the DCC's Manual of Operations for more detail on CRF submission processes.

8.1 Baseline – Required CRFs for All Enrollees (both treatment arms)

The following CRFs should be completed and submitted immediately after patient enrollment:

- Demographics & Medical History CRF
- Baseline Therapy CRF
- Confirmation of Eligibility CRF (uploaded after being signed and dated by investigator)

In addition, all pulmonary function testing reports since transplantation should be collected and maintained in the Patient Binder.

8.2 ECP Treatment Arm Patients (only) – Additional Required CRFs

Patients in the ECP Treatment Arm are also expected to have the following CRFs submitted, in addition to the CRFs noted in MOP Section 8.1:

- ECP Treatment CRF at each of the 24 ECP Treatment Visits
- Pulmonary Evaluation CRF at the following 10 timepoints
  - Day 0, which is on the day of or within one week prior to initiation of ECP
  - Day 30, which is 30 $\pm$ 7 days after the initiation of ECP
  - Day 60, which is 60 $\pm$ 7 days after the initiation of ECP
  - Day 90, which is 90 $\pm$ 7 days after the initiation of ECP
  - Day 120, which is 120 $\pm$ 7 days after the initiation of ECP
  - Day 150, which is 150 $\pm$ 14 days after the initiation of ECP
  - Day 180, which is 180 $\pm$ 14 days after the initiation of ECP
  - Day 240 which is 240 $\pm$ 14 days after the initiation of ECP
  - Day 300 which is 300 $\pm$ 14 days after the initiation of ECP
  - Day 365, which is 365 $\pm$ 14 days after the initiation of ECP
- End of Study CRF at study exit due to death, withdrawal, or completion of follow-up

8.3 Observation Arm Patients (only) – Additional Required CRFs

Patients in the Observation Arm are also expected to have the following CRFs submitted, in addition to the CRFs noted in MOP Section 8.1:

- Pulmonary Evaluation CRF for each physician-directed pulmonary function assessment (these values will automatically populate the Observation Pulmonary Evaluation Log)

- Crossover Safety Check CRF – only for patients who are crossing over to receive ECP

- End of Study CRF at study exit due to death, withdrawal, or completion of follow-up

8.4 Supplementary CRFs to be Completed As Dictated by Clinical Circumstances

Additional CRFs may need completion, in applicable clinical circumstances outlined below:

- Pulmonary Evaluation CRF – if an ECP Treatment Arm patient undergoes pulmonary function evaluation outside of the protocol-determined schedule

- ECP Treatment CRF – if an ECP Treatment Arm patient undergoes additional ECP treatment sessions beyond the first 6 months after study enrollment, or if the use of ECP therapy is prematurely discontinued (i.e. before 6 months after study enrollment)

- Change of Therapy CRF – if any immunosuppressive, anticoagulant, or antiplatelet drug is started or stopped, or if prednisone dose is changed, after study enrollment

- Serious Adverse Event CRF – if any patient develops a SAE that meets the requirements for reporting to the DCC per ECP Registry Protocol Section 6. 9

9.0 ADVERSE EVENT REPORTING

9.1 Definition of Adverse Event (AE)

An AE 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.

9.2 Definition of Serious Adverse Event (SAE)

A SAE is any AE that results in one of the following outcomes:

- 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
- Congenital anomaly, birth defect, or cancer in a neonate/infant born to a female subject

- Pregnancy abortion (accidental, therapeutic, or spontaneous)
- Medical events that do not strictly fulfill these criteria may be considered SAEs if they seriously jeopardize the subject or require aggressive intervention to prevent one of these outcomes.

9.3 Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. 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 study. Previously scheduled hospitalizations and hospitalizations needed for diagnostic or elective surgical procedures for the management of pre-existing conditions are not considered AEs.

9.4 General Reporting Requirements for 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. If an event is fatal or imminently life-threatening, the local IRB should be notified within 24 hours (Monday – Friday) of the research team's knowledge of the event. 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 ECP – 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; 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 ECP 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.

9.5 Adverse Event Worksheet and Serious Adverse Event CRF

When an Adverse Event occurs, site personnel are recommended to complete the Adverse Event Worksheet (which is also known as Section 1 of the Serious Adverse Event CRF – see Figure 1 below). To access this form, please click "Add a New Event" within that patient's entry in the EDC system.

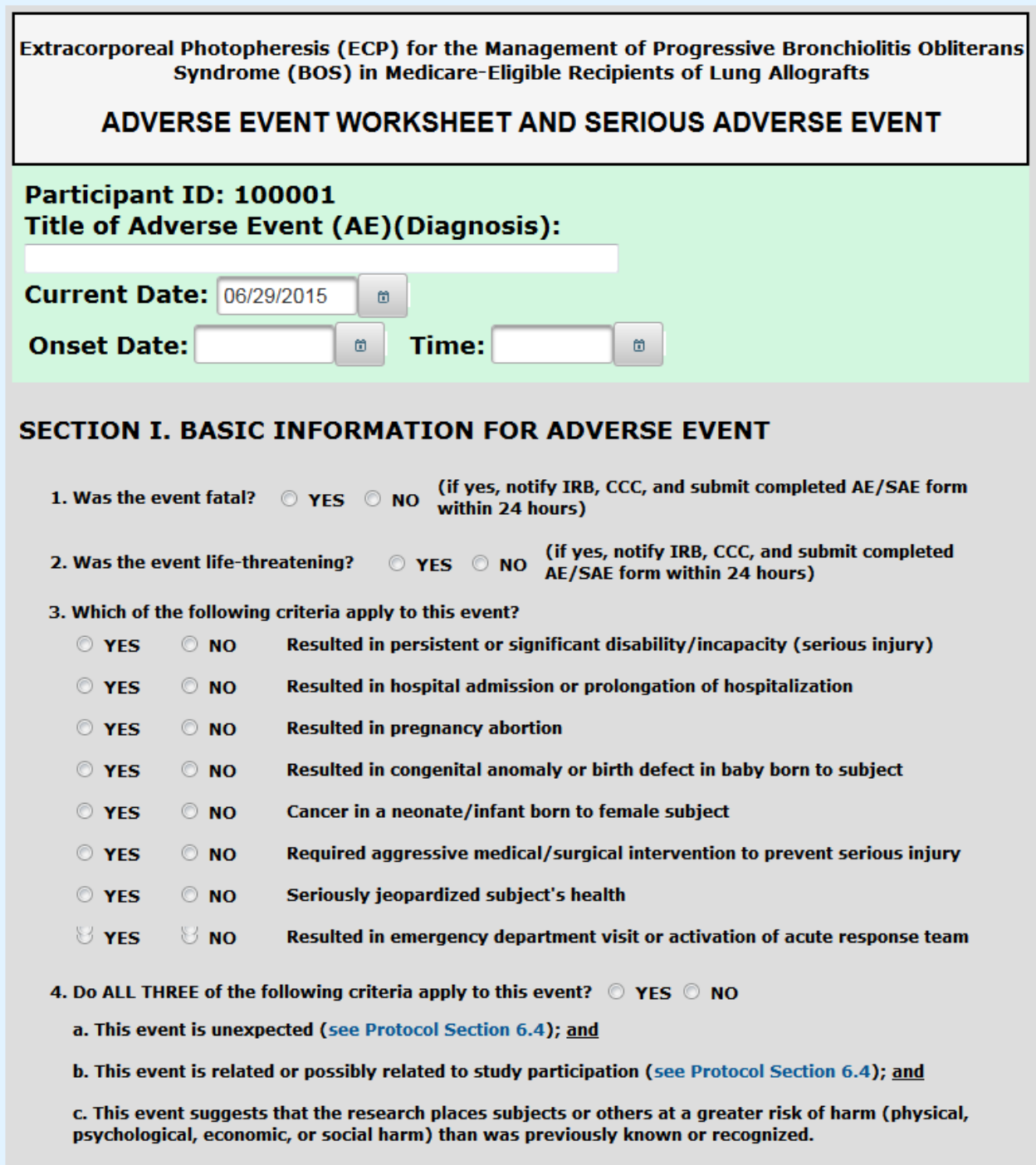
The purpose of the Adverse Event Worksheet is to help the site determine its reporting requirements for that event. The site's responses to the question items will determine:

- if the event was fatal or life-threatening (which mandates IRB reporting within 24 hours)
- if the event is a Serious Adverse Event (see below)
- if the event is an Unanticipated Problem (which mandates IRB and federal reporting)

If you answered **NO** to ALL of the questions on the Adverse Event Worksheet, then this Event is not a SAE and **should not** be reported to the Washington University team. In that case:

1. Print the worksheet. Right click on the worksheet. A pop-up box will appear. Select Print. We recommend that you have the site investigator sign and date the form, and file it in the Patient Binder along with the associated source documentation.
2. Follow your local IRB's guidelines in terms of reporting this Adverse Event to your IRB.
3. Please note that this Worksheet IS NOT SAVED within the online EDC system.

Figure 1



Extracorporeal Photopheresis (ECP) for the Management of Progressive Bronchiolitis Obliterans Syndrome (BOS) in Medicare-Eligible Recipients of Lung Allografts

ADVERSE EVENT WORKSHEET AND SERIOUS ADVERSE EVENT

Participant ID: 100001
Title of Adverse Event (AE)(Diagnosis):

Current Date: 06/29/2015

Onset Date: Time:

SECTION I. BASIC INFORMATION FOR ADVERSE EVENT

1. Was the event fatal? YES NO (if yes, notify IRB, CCC, and submit completed AE/SAE form within 24 hours)

2. Was the event life-threatening? YES NO (if yes, notify IRB, CCC, and submit completed AE/SAE form within 24 hours)

3. Which of the following criteria apply to this event?

YES NO Resulted in persistent or significant disability/incapacity (serious injury)

YES NO Resulted in hospital admission or prolongation of hospitalization

YES NO Resulted in pregnancy abortion

YES NO Resulted in congenital anomaly or birth defect in baby born to subject

YES NO Cancer in a neonate/infant born to female subject

YES NO Required aggressive medical/surgical intervention to prevent serious injury

YES NO Seriously jeopardized subject's health

YES NO Resulted in emergency department visit or activation of acute response team

4. Do ALL THREE of the following criteria apply to this event? YES NO

a. This event is unexpected (see Protocol Section 6.4); and

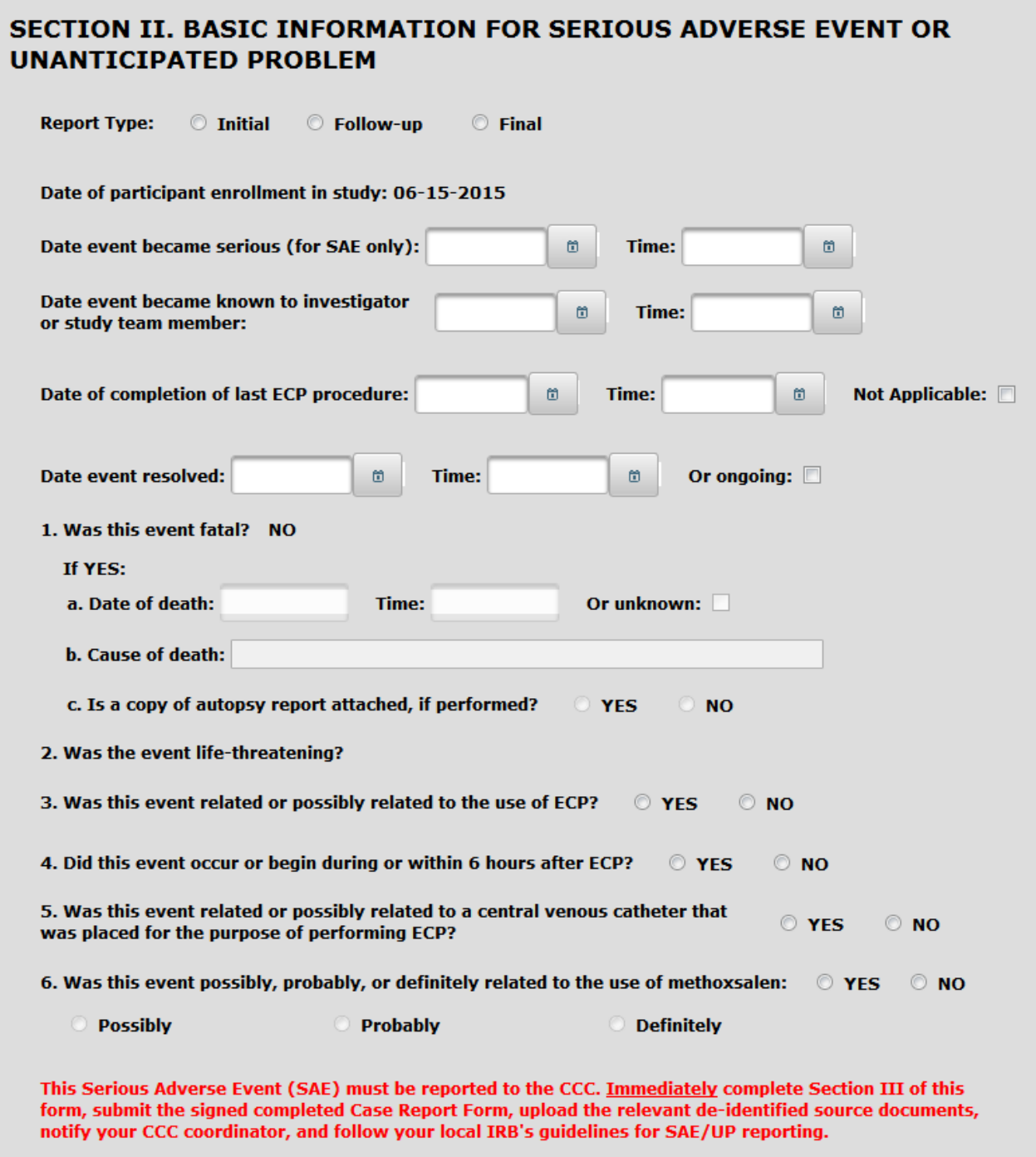
b. This event is related or possibly related to study participation (see Protocol Section 6.4); and

c. This event suggests that the research places subjects or others at a greater risk of harm (physical, psychological, economic, or social harm) than was previously known or recognized.

If, on the other hand, this Event is determined to meet the definition of a Serious Adverse Event or Unanticipated Problem, Section II of the Serious Adverse Event CRF (Figure 2 below) will open within the online system. The purpose of Section II of the CRF is to help you determine if the SAE meets the protocol's criteria for required reporting of the SAE to Washington University

(Note - if it is clear from Section I responses that the event will require reporting to Washington University, then both Sections II and Section III of the Serious Adverse Event CRF will open.)

Figure 2



SECTION II. BASIC INFORMATION FOR SERIOUS ADVERSE EVENT OR UNANTICIPATED PROBLEM

Report Type: Initial Follow-up Final

Date of participant enrollment in study: 06-15-2015

Date event became serious (for SAE only): Time:

Date event became known to investigator or study team member: Time:

Date of completion of last ECP procedure: Time: Not Applicable:

Date event resolved: Time: Or ongoing:

1. Was this event fatal? NO

If YES:

a. Date of death: Time: Or unknown:

b. Cause of death:

c. Is a copy of autopsy report attached, if performed? YES NO

2. Was the event life-threatening?

3. Was this event related or possibly related to the use of ECP? YES NO

4. Did this event occur or begin during or within 6 hours after ECP? YES NO

5. Was this event related or possibly related to a central venous catheter that was placed for the purpose of performing ECP? YES NO

6. Was this event possibly, probably, or definitely related to the use of methoxsalen: YES NO

Possibly Probably Definitely

This Serious Adverse Event (SAE) must be reported to the CCC. Immediately complete Section III of this form, submit the signed completed Case Report Form, upload the relevant de-identified source documents, notify your CCC coordinator, and follow your local IRB's guidelines for SAE/UP reporting.

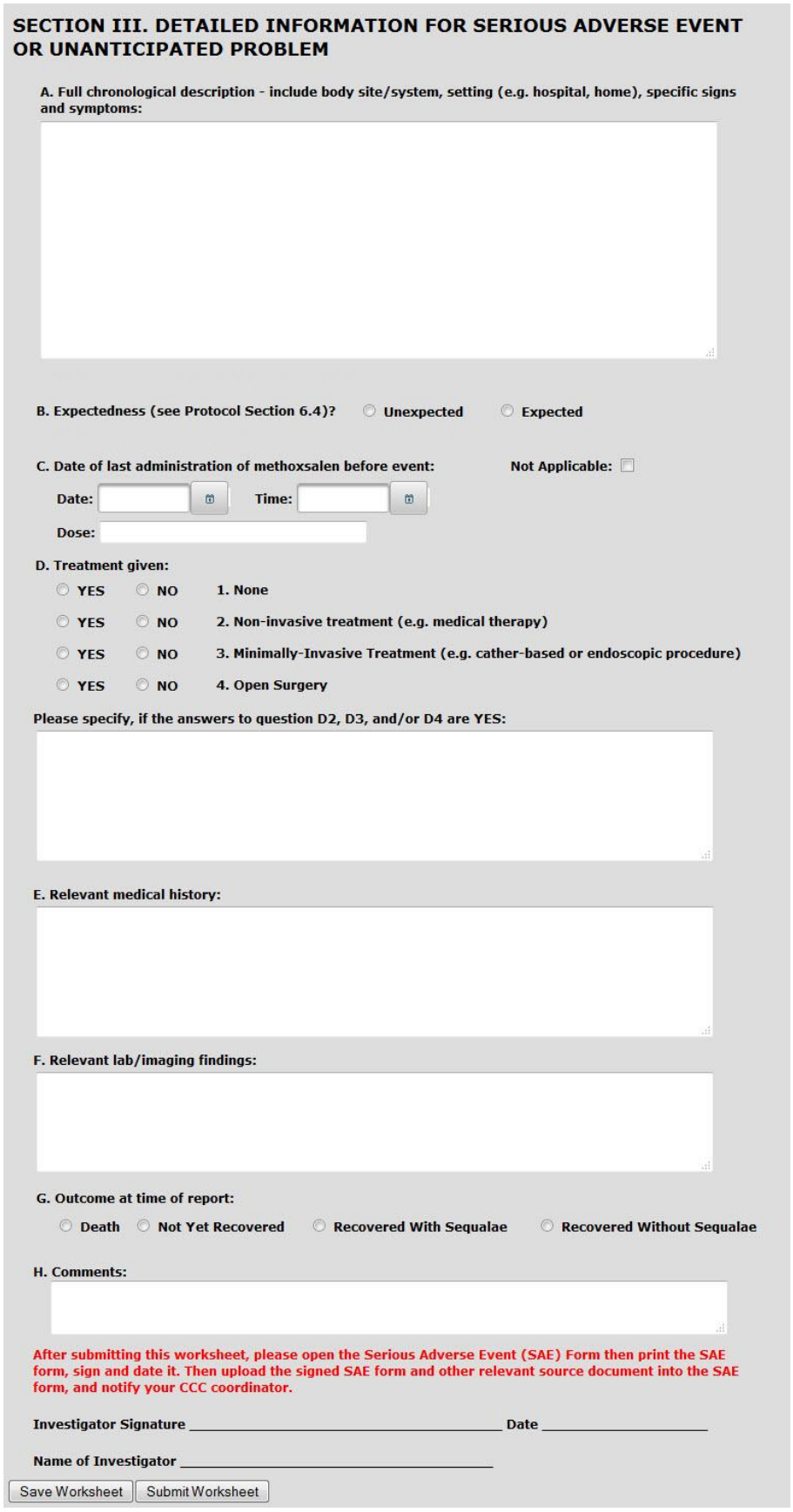
If you answered **NO** to ALL of the questions in Section II of the Serious Adverse Event CRF, then this Event **should not** be reported to Washington University. In that case:

1. Print the worksheet. Right click on the worksheet. A pop-up box will appear. Select Print. We recommend that you have the site investigator sign and date the form, and file it in the Patient Binder along with the associated source documentation.
2. Follow your local IRB's guidelines in terms of reporting this SAE to your IRB.
3. Please note that this Worksheet IS NOT SAVED within the online EDC system.

Please note that when entering data in Section II of the Serious Adverse Event CRF, there is no SAVE button. There is a 2 hour time limit on this form, after which entered data will be lost.

However, if the SAE did meet the criteria for required reporting to Washington University, Section III of the Serious Adverse Event CRF (see Figure 3 below) will open and must be completed. The entire form must be submitted within the EDC system (and source documentation uploaded) within 24 hours (Monday-Friday) of your awareness of the event; also follow your IRB's guidelines. The person submitting the form should print, sign, and date the form, and retain it in the Patient Binder. **Important: while we believe that it will be helpful to notify your CCC coordinator of SAEs when they occur, the official notifications of SAEs to Washington University must be conducted by submitting the Serious Adverse Event CRF within the EDC system and uploading the pertinent source documentation, as specified in ECP Registry Study Protocol Section 6.4. The time at which this information is submitted into EDC will be considered the official time of Washington University notification. E-mails, telephone calls, and faxes to the CCC or DCC do not constitute sufficient "notification".**

Figure 3



SECTION III. DETAILED INFORMATION FOR SERIOUS ADVERSE EVENT OR UNANTICIPATED PROBLEM

A. Full chronological description - include body site/system, setting (e.g. hospital, home), specific signs and symptoms:

B. Expectedness (see Protocol Section 6.4)? Unexpected Expected

C. Date of last administration of methoxsalen before event: Not Applicable:

Date: Time:

Dose:

D. Treatment given:

YES NO 1. None

YES NO 2. Non-invasive treatment (e.g. medical therapy)

YES NO 3. Minimally-Invasive Treatment (e.g. cather-based or endoscopic procedure)

YES NO 4. Open Surgery

Please specify, if the answers to question D2, D3, and/or D4 are YES:

E. Relevant medical history:

F. Relevant lab/imaging findings:

G. Outcome at time of report:

Death Not Yet Recovered Recovered With Sequalae Recovered Without Sequalae

H. Comments:

After submitting this worksheet, please open the Serious Adverse Event (SAE) Form then print the SAE form, sign and date it. Then upload the signed SAE form and other relevant source document into the SAE form, and notify your CCC coordinator.

Investigator Signature _____ Date _____

Name of Investigator _____

Save Worksheet Submit Worksheet

9.6 Completion of Serious Adverse Event CRF

The signed Serious Adverse Event CRF along with any relevant medical reports (de-identified to comply with HIPAA regulations) should be uploaded on the EDC system. Report the SAE to the Clinical Center's local IRB per its regulations. If the event causes death or is life-threatening, the IRB reporting must be done **within 24 hours of knowledge of the event**.

As more information becomes available, submit additional SAE information by creating a SAE Follow-Up Form on the EDC system. Once created, the SAE Follow-Up Form will automatically populate with the previously submitted information for that SAE – site personnel will only need to revise the information in the fields for which new or different information has become available. To ensure that Washington University has a record of when the information elements were submitted, changes cannot be made to SAE and SAE Follow-Up CRFs once submitted.

Once it is clear that no further information will become available, the site should complete a SAE Follow-Up Form and modify the form's status to "Final". The "Final" SAE Form must then be signed and dated by the site investigator, and re-uploaded into the EDC.

9.7 Review of SAE Categorization by CCC and DSMB

The CCC will be notified by e-mail of an SAE immediately after the SAE CRF is submitted by the site in the EDC system. The CCC will review the SAE report and source documentation and obtain any needed clarifications by telephone and/or e-mail with the Clinical Center coordinator and/or investigator(s). The CCC will forward the SAE and the appropriate source documentation to Dr. Vedantham and Dr. Despotis. Dr. Vedantham and/or Dr. Despotis will review the SAE, source documents, and the investigator's description and categorization of the SAE per the Protocol's criteria. If no additional information is required, the CCC will forward the SAE with all pertinent information to the DSMB for review. The DSMB will review and determine if the SAE was properly categorized. If not, they will provide Dr. Vedantham with a modified categorization, along with a brief written rationale for re-categorizing the SAE. In nearly all instances, the DSMB's categorization will be considered the CCC's final categorization of the SAE.

9.8 Other Reportable Events

Sites are required to report two additional categories of events to the CCC at Washington University: a) any death or serious injury (per 21 CRF 803.3) that may be associated with the use of ECP (in general, we expect that nearly all such occurrences would qualify for reporting as SAEs); and b) any complaint that is related to use of a Therakos product in the study.

10 DATA

Data collection in the ECP Registry will be performed via an Electronic Data Capture (EDC) system that is managed by the DCC. The DCC's EDC system incorporates a clinical database, a data query process, and visit completion tracking to ensure that data submission is complete, timely, accurate, and of high quality. Designated ECP Registry research personnel at the sites will be provided password-protected access to the EDC system. A secure and confidential electronic study database will be maintained by the DCC. This section summarizes some key points relating to study data; additional detail is available in the DCC's Manual of Procedures.

10.1 Case Report Form Instructions

The following general guidelines should be followed for CRF completion:

1. For ease of use, the research coordinator may print off the CRFs needed for each visit and complete the paper forms by hand. The data can then be entered into the EDC system.
2. Read all questions carefully and complete all required areas of the CRFs.
3. Follow the on-line instructions for CRF completion and the directions on the CRFs.
4. All questions must be answered on most of the CRFs. Do not leave questions blank, if possible. The EDC system will not allow some CRFs to be submitted unless most, if not all, of the questions are answered.
5. Include /upload the appropriate source documents listed on the CRFs.
6. Only Clinical Center staff designated on the Delegation of Authority Log may complete and/or sign off on CRFs.
7. CRFs available on the EDC system will need to be electronically signed by the site investigator prior to study completion, preferably at the visit level.

10.2 Data Clarifications

Entered data will be checked at the DCC for completeness, accuracy, and consistency. If any data are unclear, incomplete, or appear incorrect, a data clarification query will be generated. Each query will be represented by Query-comment next to the data in question on the CRF. A CRF Query will be used to provide a brief explanation of what is missing or needs clarification. When a CRF Query is added, the user will see CRF_Query listed under the CRF Event and Form Status columns in the EDC system - this is an indication that a query has been issued and requires a response by the site. Please respond immediately to queries as they are received. Once the correction has been made to the item being queried, the site personnel must select "Unverified" from the drop box and "Submit" the form once all queries have been addressed. Please refer to the DCC's Manual of Procedures, Section 9, for further detail.

10.3 Source Documentation

Source documents are required to support and verify subject data. The specific source documentation required by the DCC is outlined on each CRF. De-identified source documents must be identified with the patient's Participant ID Number using the source document labels (available at http://ecpregistry.wustl.edu under Investigator Resources). **To ensure compliance with HIPAA, prior to submission, please review all source documents carefully to ensure that no patient identifiers are present anywhere in the materials.** The source documents should be uploaded into EDC attached to the corresponding CRFs. Source documents include all required original records of observation, results, and activities necessary to reconstruct events and evaluate the subject. Source documents may include, but are not limited to, laboratory reports, pulmonary function testing reports, history and physical notes, consultation notes, patient progress notes, discharge summaries, clinic notes, hospital charts, and any other records or reports of procedures or diagnostic tests performed.

Source Documentation of Patient Death:

If site personnel become aware of a study patient's death, an End of Study CRF should be completed and submitted in the EDC system. The event must be reported to the DCC on the Serious Adverse Event CRF. Support documentation should include any of the items below that are available – these **de-identified** materials should be uploaded on the EDC system. De-identify this source documentation using the source document labels on the ECP Registry website at http://ecpregistry.wustl.edu under Investigator Resources. **Again, please be sure to redact any PHI within the documents that cannot be hidden by the labels.**

- Doctor's and nurse's notes in hospital or clinic chart, if applicable
- Hospital discharge summary, if applicable
- Information from subject's physician, if applicable
- Description from family or other contact, if applicable
- Other signed description that summarizes clinical presentation, duration, severity, diagnostic testing, and/or other information relevant to the fatality
- Autopsy Report, if applicable

10.4 DCC Reports to Clinical Centers

The following status reports will be available to Clinical Center personnel on the ECP Registry website on a monthly basis to optimize study and data management.

1. Monthly Trial Status Report detailing overall study enrollment with breakdown by Center.

2. CRF Status Reports outlining overdue assessments and listing any outstanding CRFs not yet received by the DCC. These reports may also be sent electronically to the applicable sites.

10.5 Data Confidentiality

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

1. The study 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 each Clinical Center with restricted access), and must be removed from all patient material sent to the DCC (e.g. source documents). Data will be identified using unique Subject Identification Numbers that provide no subject identifying information.

3. Clinical centers will require a complex password to gain access to web-based EDC system documents. Authentication (user credentials) and access privileges will be managed by DCC staff using proven, industry standard tools.

4. The DCC's EDC system will be password protected with strong encryption and will be hosted in a private cloud infrastructure managed by the DCC. The EDC system 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 ID 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.

11 SITE MONITORING

11.1 Site Monitoring Plan

The CCC at Washington University will monitor each Clinical Center to ensure that all study Protocol requirements are being met; that federal, state, and local regulations are followed; and that best patient safety practices are being followed per the study Protocol. To accomplish this, the CCC will communicate regularly with the DCC to obtain pre-specified site-specific data, and will also periodically query specific data needed to address Clinical Center issues as they arise. The CCC will evaluate the following elements of site performance, at a minimum:

1. Subject screening and enrollment, including enrollment by gender, race, and ethnicity;
2. Completeness and timeliness of reporting of serious adverse events;
3. Maintenance of HIPAA compliance;
4. Completeness of documentation in Site Regulatory Binder;
5. Completeness of documentation in Patient Binders;
6. Acquisition of informed consent in all study subjects prior to research procedures;
7. IRB documentation; and
8. Other issues of protocol adherence.

Site monitoring visits will be routinely conducted by authorized representatives of the Principal Investigator to inspect study data, informed consent forms, subjects' medical records, and CRFs, pursuant to federal and local regulations. Each Clinical Center and its site PI will permit authorized representatives of Washington University, local health authorities, and Therakos, Inc. to inspect relevant facilities and records.

11.2 Protocol Violations

Site investigators should notify the CCC of suspected protocol violations within 24 hours of becoming aware of them (Monday-Friday). The CCC will rapidly and firmly address any protocol violations. If a protocol violation is detected or suspected, the Clinical Center investigators will first be asked to provide an explanation. After reviewing the available information, the Principal Investigator will categorize protocol violations as either major or minor (per the study's Standard Operating Procedure document), and will record and track them for each site. For minor violations, an e-mail will be sent to the site investigator and research coordinator notifying them of the violation. If it is evident that the protocol is misunderstood, clarification will be provided. Major protocol violations will result in a letter from the Principal Investigator to the site investigator(s) and research coordinator, informing them of the violation and requesting a written explanation. The ECP Registry research coordinator and, as needed, the Principal Investigator will communicate with the Clinical Center personnel to confirm that a process is in place to

ensure that further protocol violations do not recur. The occurrence of either severe protocol violations or multiple protocol violations may justify either transiently or permanently halting enrollment at the site. Review of protocol violations will be a standard component of the routine CCC team meetings.

11.3 Site Regulatory Binder

Each Clinical Center must securely maintain a Site Regulatory Binder at the Clinical Center.

11.4 Patient Binder

A detailed individual Patient Binder should be maintained for each study participant to keep track of his/her involvement in the study.

11.5 Record Retention

U.S. Department of Health and Human Services (DHHS) Regulations (45 CFR 46.115) mandate that IRB records of the study must be retained for at least 3 years after study completion. The CCC and DCC reserve the right to secure data clarification & additional medical documentation on enrolled trial patients. To avoid error, the site investigator should contact the CCC before destroying any records or reports pertaining to the trial to ensure they are no longer needed.

12 SITE PAYMENT MECHANICS

Reimbursement to sites for research work completed on the ECP Registry will occur in a milestone-dependent manner. Every 3 months, the DCC will generate reports summarizing data completed at each site. This report will be provided to the CCC, and used to generate payments to the sites. Because there are many payments from multiple sites that require processing, we estimate that payment will be received by the site within 2-3 months after the end of the quarter in which each milestone was reached (i.e. in which that data was submitted).

13 POLICIES

13.1 Confidentiality

The following study subject confidentiality safeguards should be routinely followed:

- ***Data flow*** – Whenever possible, participants should be identified solely by Participant ID

Number. PHI identifiers should not be transmitted outside the Clinical Center.

- ***Forms*** – ECP Registry forms or pages containing participant identifying information should be separated from other pages of the data forms.
- ***Data disposal*** - Computer listings and other documents that contain ECP Registry participant identifying information should be disposed of in an appropriate manner.
- ***Access*** - Participant records stored in the Clinical Center should not be accessible to persons outside the center without the express written consent of the participant.
- ***Storage*** – ECP Registry forms and related documents retained both during and after study completion should be stored in a secure, fireproof location.
- ***Electronic files*** - Participant identifying information stored electronically should be maintained in an encrypted form or in a separate file.
- ***Passwords*** - Passwords that enable access to study data or participant identifying information should be changed on a regular basis.
- ***User Training*** - Study staff with access to relevant computer systems should be trained in their use and in related security measures. This training should include explanations of how to access the system securely and the importance of system security.
- ***System Testing*** - Prior to the use of a new computer system, and if it is modified, the system should be tested to verify that it performs as expected. Testing should verify that the password approach to system access performs as intended.
- ***System Backups*** - Backup copies of electronic data should be made at specified intervals, and should be stored in areas with limited access. Storage areas should have controlled temperature and humidity so that backup tapes are not damaged.

13.2 Clinical Center Staff Turnover

When new Clinical Center staff join the study, the Delegation of Authority Log must be appropriately revised. The CCC should be notified immediately so that it can ensure that new staff are properly oriented to the study and that all appropriate training is completed. Dr. Despotis must approve any proposed changes to the site PI or major co-investigators.

13.3 Study Website

The ECP Registry website will be regularly maintained and updated by DCC staff. Upon site initiation, each Clinical Center will be provided with log-in identification and password to enable its personnel to access the Investigator Resources section of the website. Important study documents, including the Protocol, MOP, and CRFs, will be posted in this area, along with additional resources that may be useful to research staff.

13.4 MOP Maintenance

This MOP will be maintained and updated periodically throughout the duration of the study by ARO personnel. Each page of the MOP will be numbered, dated, and will display a version number. Updated versions will be accompanied by a track changes version that highlights the changes. In this fashion, the MOP will serve as a history of the project, documenting the time and nature of any changes in procedures and policies. The MOP will be continuously reviewed by study staff to ensure its accuracy. If any procedures are subsequently changed or modified, the MOP will be updated and the changes will be distributed to the Clinical Center coordinators.