Clinical Trial Protocol

Full Title:	Extracorporeal Photopheresis in the treatment of Chronic Lung Allograft Dysfunction: a randomised controlled trial
Short Title/Acronym:	E-CLAD UK
Protocol Version Number & Date:	**V2.0 14 October 2022**
Previous Versions:	

Statement:

This protocol has regard for the HRA guidance.

RESEARCH REFERENCE NUMBERS

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EudraCT Number:	2022-002659-20
NHS REC Reference:	22/EM/0218
Research Registry & References:	

RESEARCH SPONSOR

Sponsor Name:	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Sponsor Reference:	**R&D10000/NU-000947**

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PROTOCOL APPROVAL SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted. The undersigned agree to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, Good Clinical Practice (GCP) guidelines, the relevant Standard Operating Procedures and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

Representative of the Research Sponsor

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Position:

Signature: Date:

Chief Investigator (CI)

Name: Andrew John Fisher

Position: Professor of Respiratory Transplant Medicine

Signature: Date:

Statistician

Name:

Position:

Signature: Date:

Newcastle Clinical Trials Unit (NCTU)

Name:

Position:

Signature: Date:

PROTOCOL ACCEPTANCE SIGNATURE PAGE

Short Trial Title: E-CLAD UK

Principal Investigator

I have carefully read and understood protocol version 1.0. I agree to conduct the trial in compliance with Good Clinical Practice and all required regulatory requirements.

Name:

Position:

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TRIAL SUMMARY

Trial Title	Extracorporeal Photopheresis in the treatment of Chronic Lung Allograft Dysfunction: a randomised controlled trial
Acronym	E-CLAD UK
Clinical Phase	Phase II
Summary of Trial Design	Prospective, 2-arm, randomised, open-label, multicentre clinical trial performed in all 5 of the designated adult lung transplant centres in the UK
Summary of Participant Population	Adults, 16 years or over who have received a bilateral lung or heart and bilateral lung transplantation that fulfil the ISHLT diagnostic criteria for Chronic Lung Allograft Dysfunction
Planned Sample Size	90
Treatment Duration	20 weeks ECP therapy
Follow Up Duration	24 weeks
Planned Trial Period	36 months recruitment 24 weeks follow up 6 months close down/data lock/analysis

	Objectives	**Outcome Measures**
Primary	To determine if extracorporeal photopheresis (ECP) therapy plus standard of care (SOC) is more effective at improving or stabilising lung function in lung transplant recipients with chronic lung allograft dysfunction (CLAD) compared to SOC alone	Composite responder outcome of lung function stabilisation derived from change in Forced Expiratory Volume (FEV1) and Forced Vital Capacity (FVC) at 12 and 24 weeks compared to baseline at study entry.
Secondary	Change in rate of decline in lung allograft function before randomisation and up to 24 weeks after randomisation	FEV1 and FVC
	Absolute change in lung allograft function	FEV1 and FVC
	Change in exercise capacity at 24 weeks	6-minute walk test

	Change in Quality of Life measurements at 24 weeks	EQ-5D-5L and SF-36 v2 questionnaires
	Change in Disease severity	ISHLT CLAD Stage
	Survival at 24 weeks	
Mechanistic	To identify changes in immune responses occurring in those responding to ECP therapy compared to non-responders to ECP and untreated controls to identify a beneficial mechanism of action	Immune cell phenotyping transcriptomics analysis of circulating leucocytes, serum cytokine analysis and measures of immune tolerance and apoptosis
	To determine if CLAD phenotype, clinical factors or immune and inflammatory markers in blood alone or in combination can predict likelihood to benefit from ECP	Regression models with responder/non-responder as an outcome and each potential clinical factor or biomarker included as a baseline covariate
Intervention	Nine cycles of ECP therapy administered at 0, +2, +4, +6, +8, +10, +12, +16 and +20 weeks. Each cycle consists of 2 ECP treatments on consecutive days	
Formulation, Dose & Route of Administration	Methoxsalen (UVADEX®) 20 micrograms/ml solution for blood fraction modification used in conjunction with the THERAKOS CELLEX Photopheresis System®	
	Administered via injection into the recirculation bag of the THERAKOS CELLEX Photopheresis System® prior to the photoactivation phase of ECP treatment	
	Dose 0.017mls methoxsalen per ml blood volume treated at ECP	
	Total dose administered is calculated according to buffy coat treatment volume per individual ECP treatment	

Contents

GLOSSARY OF ABREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
AR	Adverse Reaction
ATS	American Thoracic Society
BOS	Bronchiolitis Obliterans Syndrome
BTRU ODT	Blood and Transplant Research Unit in Organ Donation and Transplantation
CA	Competent Authority
CI	Chief Investigator
CLAD	Chronic Lung Allograft Dysfunction
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTU	Clinical Trials Unit
CTIMP	Clinical Trial of an Investigational Medicinal Product
DLCO	Total diffusing capacity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DSUR	Development Safety Update Report
ECP	Extracorporeal Photopheresis
eCRF	Electronic Case Report Form
EDTA	blood sample collection tube
eGRF	estimated glomerular filtration rate
EMA	European Medicines Agency
EME	Efficacy and Mechanism Evaluation
EQ-5D-5L	Health-Related Quality of Life (Questionnaire)
ERS	European Respiratory Society
EU	European Union
EudraCT	European Clinical Trials Database
FBC	Full Blood Count
FEF25-75	Forced Expiratory Flow between 25% and 75% of vital capacity
FEV1	Forced Expiratory Volume in 1 second

FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HRA	Health Research Authority
HRCT	High-Resolution Computed Tomography
HSCT	Hematopoietic Stem Cell Transplantation
HTA	Human Tissue Authority
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
IDMC	Independent Data Monitoring Committee
IDMEC	Independent Data Monitoring and Ethics Committee
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISHLT	International Society for Heart and Lung Transplantation
ISRCTN	International Standard Randomised Controlled Trials Number
IV	Intravenous
KCO	Transfer factor for Carbon Monoxide
LFT	Liver Function Test
MA	Marketing Authorisation
MG	Milligrams
ML	Millilitres
MHRA	Medicines and Healthcare products Regulatory Agency
6MWT	Six Minute Walk Test
NCTU	Newcastle Clinical Trials Unit
NENC	North East and North Cumbria
NHS	National Health Service
NIHR	National Institute for Health Research
NRES	National Research Ethics Service
NUTH	Newcastle upon Tyne Hospitals (NHS Foundation Trust)
PFT	Pulmonary Function tests
PI	Principal Investigator
PIS	Participant Information Sheet
PMH	Previous Medical History

PSS	Patient and Public Involvement
PPI	Personal Social Services
QA	Quality Assurance
QALY	Quality Adjusted Life Year
QC	Quality Control
R&D	Research & Development
RAS	Restrictive Allograft Syndrome
RA	Regulatory Authority
RCT	Randomised Control Trial
REC	Research Ethics Committee
RNA	blood sample collection tube
RSI	Reference Safety Information
RV	Residual Volume
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAP	Statistical Analysis Plan
SF-36	Health-Related Quality of Life (Questionnaire)
SOC	Standard Of Care
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TLC	Total Lung Capacity
TLCO	Transfer capacity of the Lung for Carbon Monoxide
TLI	Total Lymphoid Irradiation
TMG	Trial Management Group
TSC	Trial Steering Committee
U&E	Urea and electrolytes
USM	Urgent Safety Measure
UV	Ultraviolet
UVA	Ultraviolet A
VA	Alveolar Volume
UK	United Kingdom

1. BACKGROUND AND RATIONALE

1.1 Background

Lung transplantation is the only treatment offering a meaningful improvement in survival and quality of life to selected patients with life threatening chronic lung disease. Across the world, approximately 5000 lung transplants are performed each year: almost 200 of these in the UK. However long-term survival after lung transplantation is significantly poorer than for other organ transplants including heart, liver, and kidney. Data from the International Society for Heart and Lung Transplantation (ISHLT) registry show the median survival after lung transplantation is just 6 years (1). The main reason for this reduced survival is the development of progressive immune-mediated damage to the lung allograft despite the use of powerful immunosuppressive drugs. This damage causes chronic inflammation and fibrosis in two patterns either around the airways causing airway obstruction, known as bronchiolitis obliterans syndrome (BOS); or within the lung parenchyma affecting alveolar structure, known as restrictive allograft syndrome (RAS). These can co-exist in a mixed phenotype (2). These phenotypes are grouped under the umbrella term CLAD which was recently redefined by the ISHLT in an international consensus statement (3). CLAD is the commonest cause of death after the first post-transplant year, affecting at least 10% of recipients every year. This means more than 50% of recipients will develop CLAD within 5 years of their transplant. CLAD can progress rapidly in months causing lung function decline, respiratory failure, and death; it often returns recipients to levels of disability and mortality risk they experienced immediately before transplant (4).

The immune mechanisms driving CLAD are not well understood and at present no treatments have been proven to reverse or reliably halt the damage and loss of lung function (5). About 30% of those with suspected CLAD respond to long-term macrolide antibiotic use by improving or stabilising lung function, although this benefit may be temporary (6). Recently, the official 2019 ISHLT CLAD consensus statement removed this group of macrolide responders from its CLAD definition and CLAD is now only diagnosed if lung function continues to decline despite an appropriate duration trial of azithromycin therapy (4). Retransplantation is currently the only hope for those with severe CLAD, yet many recipients are not suitable due to presence of co-morbidities such as renal dysfunction, frailty, and colonisation with resistant organisms (7). There is an urgent need to identify new treatments that can arrest the alloimmune mechanisms driving CLAD as early as possible, preserving longevity and quality of life whilst also removing the need for possible retransplantation.

Current SOC for CLAD is supportive, focusing on supplemental oxygen to treat hypoxaemia and dyspnoea, palliative opiates, and anxiolytics to treat dyspnoea and distress, as well as social and psychological support to help with the increasing levels of disability. Therapeutics tested in CLAD include switching between classes of immunosuppressive drugs, immunotherapy with monoclonal antibodies, inhaled immunosuppression, total lymphoid irradiation, anti-fibrotic and anti-inflammatory drugs, mesenchymal stem-cells and ECP (8). A systematic review of therapy options for CLAD suggests possible slowing of disease with use of ECP or total lymphoid irradiation (TLI) in single centre non-randomised studies; however, none have provided robust high-quality evidence to change routine practice (9).

ECP, a potential treatment tested for CLAD, modulates the recipient's immune system. ECP involves connecting a patient via an intravenous line to an apheresis machine that separates leukocytes from whole blood in a buffy coat. The red cells are immediately returned to the patient while the leukocytes are treated with methoxsalen, a photosensitising agent and then exposed to ultraviolet A (UVA) light to induce apoptosis. The pre-apoptotic leukocytes are then returned to the recipient's circulation where they exert immunomodulatory effects. The entire process can be automated within the latest generation ECP machines. In many cases, ECP therapy can be delivered through peripheral cannulas

although some patients require a tunnelled central venous catheter for reliable vascular access. ECP is given as an initial 3–6-month course of treatment and is used widely internationally to treat acute and chronic graft vs host disease after haematopoietic stem cell transplantation (HSCT) and in cutaneous T-cell lymphoma (10).

1.2 Rationale

A systematic review using full text search terms for [ECP] + [lung transplantation] or [CLAD] or [BOS] or [RAS] in PubMed yielded 5 reviews, 2 mechanistic studies and 9 relevant clinical studies. These studies used ECP in lung transplant recipients with CLAD and showed promise in slowing or halting its progression (11). However, these are universally single centre retrospective studies conducted over prolonged periods of time while other aspects of care were also evolving. There was a lack of proper untreated controls and ECP was offered to only selected patients with CLAD. None of these studies were performed in the UK in an NHS setting, so high-quality evidence of the efficacy of ECP in CLAD treatment has not yet been established. The proof of concept for use of ECP in CLAD comes from 4 larger studies (described below) that represent a collective experience of 223 lung transplant recipients with CLAD, including RAS and BOS phenotypes. Of the 4 studies, 3 reported a clinical response ranging from 54-61%. None were conducted as a prospective randomised controlled trial (RCT) and all have limitations of bias in patient selection.

Morrell et al (12) reported retrospective outcomes on 60 patients treated with ECP for progressive BOS. They compared rate of decline in FEV1 for 6 months before and after commencement of ECP showing a significant reduction in the rate from -116 mls/month to -28.9 mls/month (p=0.0001). 25% of treated patients showed an increase in lung function within 6 months. There was a 13% rate of hospitalisation for line sepsis, including 1 death, but this was limited to only those with long-term indwelling apheresis catheters; no line infections were reported in those treated through peripheral cannulation. There was no control group and selection of patients for treatment implied bias.

Jaksch et al (13) reported a single centre experience of treating 51 BOS patients with ECP. 61% of those treated demonstrated improvement or stabilisation in FEV1 defined as <5% decline over the first 6 months of treatment. ECP treatment response was also associated with an improved survival and reduced need for retransplantation compared to patients with BOS not getting ECP and those not responding to ECP. There was a selection bias as only 26.2% of BOS patients at this centre received ECP. No adverse events (AEs), including serious infections, were reported.

Greer at al (14) reported a retrospective study of 64 CLAD patients over 4 years who, despite use of azithromycin continued to lose graft function and were treated with ECP. 54% responded to treatment with either an increase or <10% decline in FEV1. They found responders experienced a significant survival benefit with median survival being 401 days compared to 133 in non-responders. The RAS phenotype and rapid decliners were less likely to respond. The ECP regimen and schedule used in this study is very similar to that in the E-CLAD UK protocol.

Del Fante et al (15) reported a retrospective study of 48 patients with CLAD identified over 10 years who received ECP. They compared their outcomes with 58 CLAD patients not treated with ECP. The groups were not randomly allocated with many factors determining who received treatment; 30% had RAS and 70% BOS. They used an off-line or manual ECP protocol rather than an automated system as is planned in the E-CLAD UK study proposal. They showed a significant reduction in the rate of decline in FEV1 in the first 6 months after ECP was commenced compared to 6 months before ECP. 60% of patients treated with ECP stabilised their FEV1 defined as <10% decline within 6 months. There were no significant complications reported.

The exact mechanism of immunomodulation with ECP is not fully understood and published literature exploring this is limited to small uncontrolled studies. The proposed paradigm is that DNA cross-linking occurs in methoxsalen-treated leukocytes exposed to UV light causing apoptosis after return to the patient's circulation. The presence of the apoptotic cells then exerts effects on other immune cells driving the beneficial actions (16). Mechanistic studies of ECP in CLAD are extremely limited. A study of 5 patients with the BOS phenotype of CLAD, showed 3 who responded to ECP had a modest increase in regulatory T-lymphocytes (17). A further study in the BOS phenotype only showed a fall in pro-inflammatory cytokines and a reduction in donor-specific antibodies (18). There have been no studies which have systematically evaluated the immunological changes in circulating proteins, immune cell numbers, phenotype, and activation status to identify both mechanisms of action and potential markers which predict likelihood of a patient with CLAD responding to ECP.

1.3 Risk Assessment

ECP is indicated for the treatment of acute and chronic graft vs host disease after haematopoietic stem cell transplantation (HSCT) and in cutaneous T-cell lymphoma. For the purposes of this protocol, ECP will be used in patients with Chronic Lung Allograft Dysfunction (CLAD).

This trial is categorised as:

- Type B = somewhat higher than the risk of standard clinical care

A risk assessment has been completed – this has been reviewed by the Trial Management Team, Chief Investigator and Sponsor.

This study involves bilateral lung transplant patients who develop CLAD. Participants will be randomised to receive either standard of care alone or standard of care plus ECP. Any participants that are classed as non-responders during the week 12 assessment will have the option to be withdrawn from the trial and receive further rescue treatment outside of the study. As this can take time to arrange participants in the ECP arm can continue with the ECP treatment as part of the trial until further treatment is ready. Likewise, if there are no other treatment options available and it is felt appropriate clinically to continue ECP despite a decline in lung function, this is also possible.

For both groups, treatment response will be formally assessed at 12 weeks. However, if there is rapidly progressive CLAD as per protocol before the 12 Week Assessment, participants may leave the trial earlier and access alternative rescue treatments.

2. OBJECTIVES AND OUTCOME MEASURES

2.1 Primary Objective

To determine if ECP therapy plus SOC is more effective at stabilising lung function in lung transplant recipients with CLAD compared to SOC alone.

Lung function stabilisation will be derived from change in FEV1 and FVC at 12 and 24 weeks compared to baseline at study entry. The primary outcome measure is a composite responder outcome, which is defined as both 'lung function stabilisation' from baseline to 24 weeks and 'no rapid decline' as measured from baseline to 12 weeks (see section 7 for definitions).

2.2 Secondary Objectives

To determine how the treatment strategies of ECP therapy plus SOC and SOC alone affect the following outcomes over a 24-week period:

- Change in rate of decline in lung allograft function between before randomisation (available from clinical records) and up to 24 weeks after randomisation, measured by change in FEV1 and FVC (litres/month).
- Absolute change in lung allograft dysfunction from baseline to 24 weeks, measured by FEV1 and FVC (litres).
- Change in exercise capacity from baseline to 24 weeks measured by distance walked (metres) during a 6-minute walk test.
- Change in disease severity from baseline to 24 weeks measured by ISHLT CLAD Stage (1-4).
- Change in health-related quality of life from baseline to 24 weeks measured by SF-36 v2 and EQ-5D-5L.
- Survival at 24 weeks after randomisation (end of study).
- Adverse events (AEs) and Serious adverse events (SAEs) from randomisation to 24 weeks.

2.3 Sub-Studies

2.3.1 Mechanistic Sub-study

A mechanistic evaluation of participants' immune responses will be undertaken to understand how these change before and after commencing ECP therapy and identify if there are any molecular or cellular markers at baseline which help predict which patients treated with ECP are more likely to respond.

Mechanistic Objectives

- To characterise immune responses occurring in recipients responding to ECP compared to non-responders, and those receiving SOC alone, to identify potential mechanisms of action.
- To determine if CLAD phenotype, clinical factors, or immunological markers in blood can predict who will benefit from ECP.

Further details of outcome measures being collected to answer mechanistic objectives are detailed in 6.1.2.

2.3.2 Qualitative Sub-study

A qualitative sub-study will be conducted to critically examine the perceptions and experiences of patients living with CLAD and their experiences and understandings of ECP therapy.

Individual focused semi-structured interviews will be carried out with up to 30 patients with CLAD including 20 who have experienced ECP. Interviews will provide new insights about patient experiences of living with CLAD as well as providing valuable information about experiences of ECP therapies which will inform future wider implementation. This sub-study will explore:

- Patients' experiences of living with CLAD and its impact on their everyday lives.
- Patients' prior understandings of CLAD or the possibility of this or "chronic rejection."
- Patients' understandings and views of current treatments for CLAD.
- Patients' views, experiences and understanding of ECP therapy.

2.3.3 Health Economic Evaluation

A health economic evaluation will be undertaken in parallel with the main E-CLAD UK trial to demonstrate if ECP represents an effective use of health service resources in this patient population.

No additional data will be required from sites for this.

This work is funded separately to the EME NIHR funding and does not form part of the NIHR funded work and it will be reported separately to the main trial.

Please see Appendix 3 for more information regarding the health economic evaluation.

3. TRIAL DESIGN

3.1 Summary of Trial Design

E-CLAD UK is a phase II, prospective, two-arm, randomised, open-label, multicentre clinical trial to evaluate the efficacy of ECP in stabilising lung function in lung transplant recipients with progressive CLAD.

Consenting patients who fulfil inclusion criteria will be randomised 1:1 to receive either SOC (control arm) or SOC plus a 20-week course of ECP. Patients randomised to receive ECP will be administered 18 treatments in 9 cycles of ECP over 20 weeks.

Follow up will be for a total of 24 weeks from commencing the intervention (4 weeks after the last cycle of ECP in the intervention arm). Follow up visits will be conducted for all participants at 4, 8, 12, 16, 20 and 24 weeks.

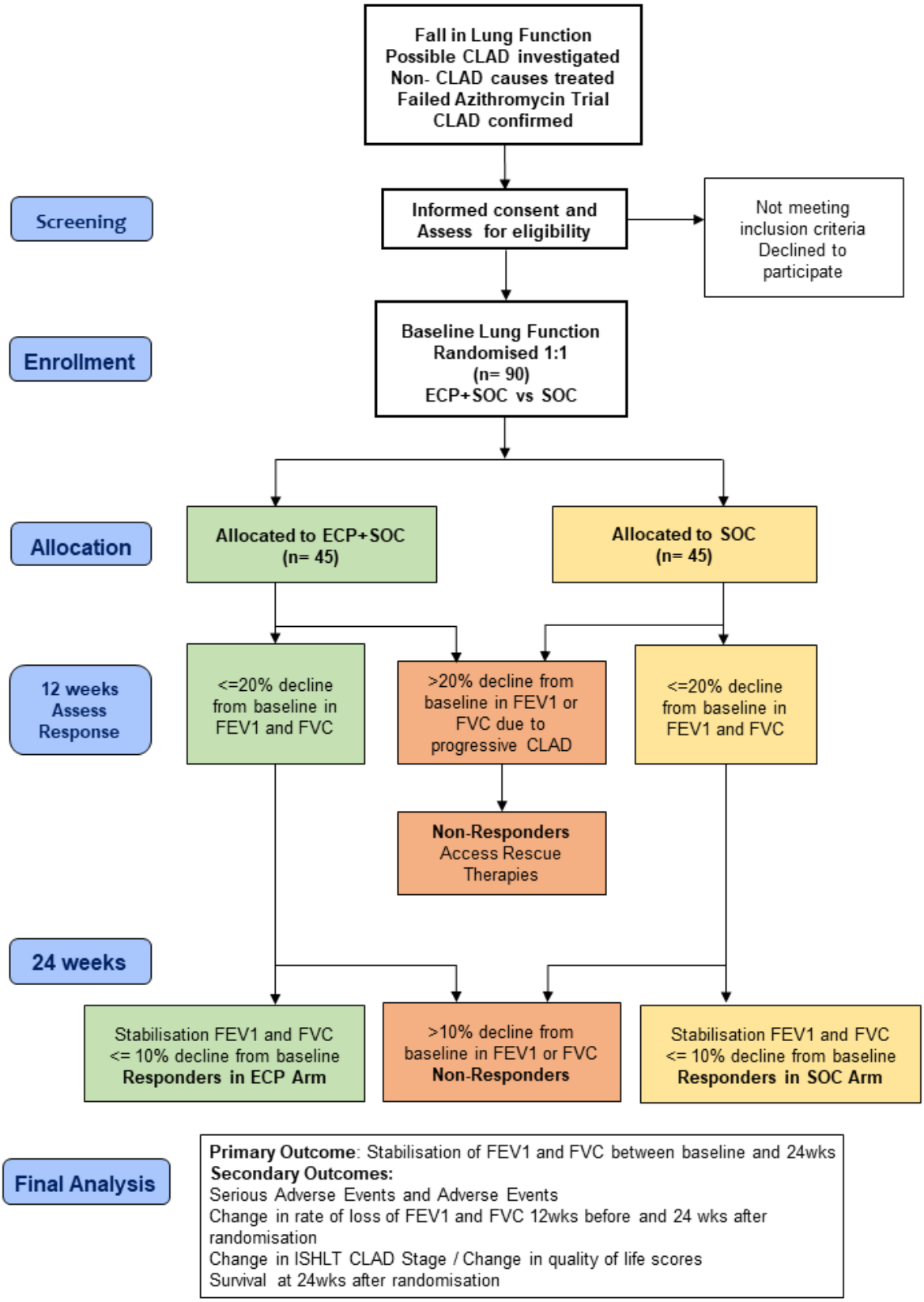
Participants in both arms will be assessed at 12 weeks to determine if they are responding to treatment. Participants who experience a >20% fall in FEV1 or FVC from baseline to 12 weeks **due to progressive CLAD** will be deemed non-responders.

3.2 Trial Setting

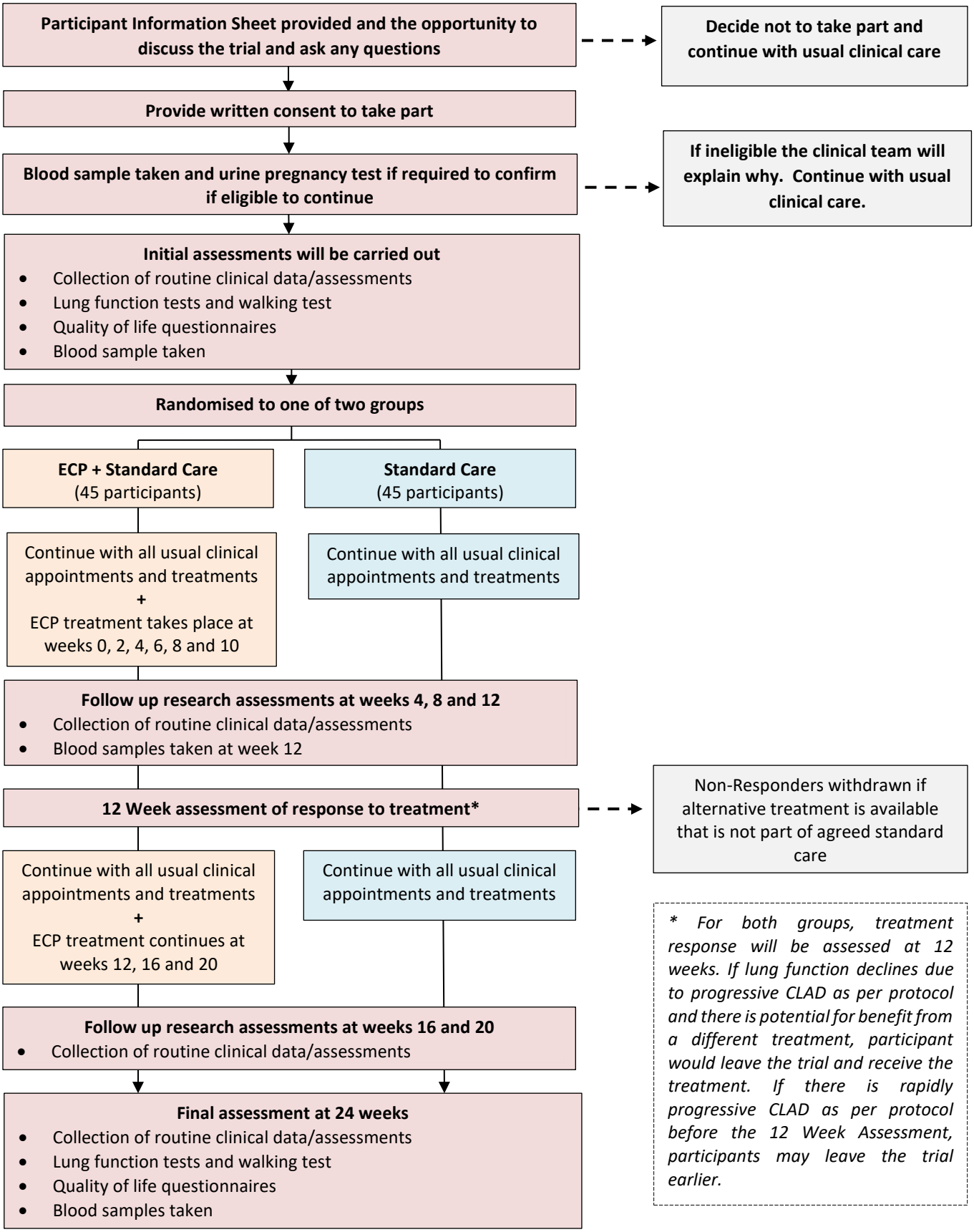
The trial will be performed in a tertiary care setting involving all five of the designated adult lung transplant centres in the UK. This will allow all adult UK bilateral lung transplant patients who develop CLAD to learn about the trial and decide if they wish to participate.

3.3 Flow Charts of Study Design and Research Activity

3.3.1 Overview of Study Design



3.3.2 Flow Chart of Research Activity



3.4 Primary and secondary outcome measures/endpoints

3.4.1 Primary outcome measure

Lung function stabilisation will be derived from change in FEV1 and FVC at 12 and 24 weeks compared to baseline at study entry. At baseline and 24 weeks FEV1 and FVC will be taken from Full Pulmonary Function Tests (PFT) carried out as a research assessment. At 12 weeks FEV1 and FVC values will be taken from those collected as part of routine clinical assessment.

Full Pulmonary Function Tests

Full pulmonary function tests to include FEV1, FVC, FEF25-75, Flow-volume loop, TLC, RV, Va, TLCO and KCO should be performed in a fully accredited lung function laboratory by or under the close supervision of a qualified pulmonary physiologist. Results should be provided as absolute values, % predicted values and z-scores. All spirometry should be performed according to ATS/ERS standards. If a bronchodilator response is performed, then post-bronchodilator FEV1 and FVC values should be reported.

Routine spirometry tests

Routine clinic spirometry as collected regularly in the transplant clinic should be performed in accordance with usual clinical practice in the transplant centre by a trained individual able to ensure adequate reproducibility/quality control of the test and reporting of absolute values of FEV1 and FVC. Tests can be performed in either an accredited lung function laboratory or using a desktop or handheld spirometer as long as adequately supervised. Interpretation of the routine spirometry will be by the participant's lung transplant physician. Home spirometry results performed by participants using a handheld spirometer already in their possession can be used in place of routine clinic spirometry if it is not possible for the participant to attend. In such cases the principal investigator must be confident the participant is trained in its use and able to perform reproducible spirometry. Home spirometry cannot be used to replace the baseline and end of study full pulmonary function tests or the 12-week assessment time point.

3.4.2 Secondary outcome measures

Spirometry Tests

FEV1 and FVC values collected as part of routine clinic spirometry and research pulmonary function tests along with historical clinical spirometry data from medical records will be used to calculate rate of decline and absolute change in lung allograft dysfunction. Calculation of rate of change will require at least 3 measurements from the period leading up to randomisation (maximum 26 weeks but ideally within 12 weeks) and the 24 weeks after randomisation. Recordings should be performed as detailed in section 3.4.1.

6 Minute Walk Test (6MWT)

Change in exercise capacity will be measured from baseline to 24 weeks using the change in the 6MWT distance. The 6MWT is a self-paced 6-minute walk recording the distance walked in metres (19). The walking track will be standardised for each site with all participants receiving standardised instructions and encouragement. An oximeter will be attached to the participant during the walk for continuous monitoring of oxygen saturations and heart rate. The 6MWT test will be performed and recorded once for the baseline and final assessments. If there are technical issues which affect the quality of the test or reliability of the result, then it will be repeated after a period of 30 minutes between the two walks to allow the oxygen saturation and heart rate to return to resting levels.

The following measurements will be collected during the 6MWT:

Total Distance Walked during the 6 minutes in metres

Resting oxygen saturation (%) at start, lowest saturation during the test and saturation at end

Number of stops and amount of time spent stopped

Degree of breathlessness using the Borg Score (0-10)

EQ-5D-5L

The EQ-5D-5L will be collected at baseline and 24 weeks to assess change in participant reported quality of life.

The EQ-5D-5L general health questionnaire evaluates five domains (-5D), which include: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (20). This is a two-page questionnaire that consists of five dimensions, with the responses recorded at five levels (5L) of severity (no problems; some problems or extreme problems). The second page consists of a standard vertical 20cm visual analogue scale (EQ-5D VAS) which is transformed to a scale of 0 to 100 measuring current health-related quality of life. Each participant's health state, derived from the EQ-5D, will be measured before and after the intervention period determine the change in their health gain or loss.

SF-36 V2

The SF-36 V2 will be collected at baseline and 24 weeks to assess change in participant reported health status.

The SF-36 medical outcomes study questionnaire short form health survey involves 36 questions grouped to eight scales of health including: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, social role functioning, and mental health (21). Responses are recorded either on 5-point scales, 3-point scales or as dichotomous (yes/no) items. Sections are then scored on the weighted sums of the questions in each section in a scale of 0 to 100. These are combined to produce two psychometrically based physical and mental health summary measures.

Case Report Form (CRF)

CRFs will be used at each assessment time point to capture change in CLAD symptoms, changes to medications and routine clinical care and new interventions. Changes to CLAD stage will be captured as well as results of routine bloods, Chest X-rays, PFT's and other relevant assessments. All aspects of standard of care received will be collected for all participants.

ECP CRF's will capture all relevant details associated with ECP treatment including compliance and deviations from the planned intervention.

CRF's will be used to capture any deviation and adverse events in all participants.

The majority of CRFs will be electronic and completed via the online trial database. For those sites where the ECP unit sits separately to the transplant research team, a paper CRF will be provided for completion. Once completed this paper CRF must be provided to the relevant research team for data entry into the eCRF. The paper CRF must be kept, with the original filed in the Investigator Site File and a copy filed/uploaded to the participants medical notes at the research site.

4. TRIAL PARTICIPANTS

Patients aged 16 and over who have received a bilateral (a.k.a. single sequential) lung or heart and (bilateral) lung transplantation that fulfil the ISHLT 2019 diagnostic criteria for CLAD.

Eligibility must be assessed by a medically qualified doctor and this assessment documented in the participant's medical notes. Only personnel formally delegated by the Principal Investigator (PI) to assess eligibility may perform this task.

Patients are eligible for the trial if **all** the following inclusion and exclusion criteria apply.

4.1 Inclusion Criteria

- Adults (≥16 years of age) with body weight ≥30 kg.
- Bilateral lung or heart and (bilateral) lung transplant recipients.
- Confirmed diagnosis of CLAD stages 1, 2 or 3 as per ISHLT 2019 consensus definition (see section 7 for definition).
- New CLAD diagnosis or prior diagnosis with evidence of current progressive disease.
- Exclusion of non-CLAD causes for decline in lung function by high-resolution computed tomography (HRCT) thorax and bronchoscopy +/- transbronchial biopsy within 12 weeks of first CLAD diagnoses.
- Adequate treatment of potential non-CLAD causes of a decline in lung function (e.g. acute cellular or acute humoral rejection, infections, airway anastomotic strictures and medical treatment for gastroesophageal reflux).
- Progressive decline in FEV1 (≥10%) while on azithromycin for ≥6 weeks.
- Capacity to provide written informed consent.
- A minimum of 2 recorded FEV1 and FVC measurements (including home spirometry) obtained during the 26 weeks preceding consent*. Measurements must be at least 3 weeks apart with the last measurement at least 3 weeks prior to consent

* FEV1 and FVC values collected as part of routine clinic spirometry and research pulmonary function tests along with historical clinical spirometry data from medical records will be used. Ideally readings should be from the preceding 12 weeks but up to 26 weeks prior to consent is acceptable. These will ideally have been collected at clinical appointments, but home spirometry readings are also acceptable.

4.2 Exclusion Criteria

- Single lung transplant recipients.
- Female patients who are breastfeeding, pregnant or planning to become pregnant during the timeframe of study participation.
- Current treatment with or past history of TLI completed within the last 12 months.
- ≤1-month wash-out from any other investigational therapies for CLAD.
- Inability to perform lung function tests or adhere to study protocol as judged by supervising clinician.
- History of Hematopoietic Stem Cell Transplantation (HSCT).
- Patients who are on a retransplant waiting list.
- Current participation in another interventional clinical trial, or participation in a clinical trial of an investigational agent in the previous 4 weeks from consent.

- Patients with inadequate vascular access (peripheral or central) options to perform ECP.
- Any contraindication to receiving ECP. These include:
    - Previous allergic reaction to methoxsalen, another psoralen compound, or any of the other UVADEX® ingredients.
    - Co-existing untreated skin cancer* (melanoma, basal cell or squamous cell cancer).
    - Any disease which involves sensitivity to light such as porphyria, systemic lupus erythematosus or albinism
    - Previous removal of spleen
    - Blood clotting disorder or an increased white blood cell count >25x10^9 per litre.
    - Significant heart disease or severe anaemia causing inability to tolerate blood volume shifts associated with ECP.
    - Aphakia or lens removed from either eye (unless already blind in eye without a lens).
    - Sexually active men and women of childbearing potential unless adequate contraception is used during treatment.

*Patients with co-existing treated skin cancer should be assessed and counselled on the balance of risks of harm from their skin cancer after exposure to methoxsalen or from their CLAD diagnosis in determining if this constitutes an exclusion criterion.

NB: Enrolling a patient onto the trial who does not meet the inclusion/exclusion criteria is considered a protocol waiver and is in breach of Regulation 29 (SI 2004/1031) of the Medicines for Human Use (Clinical Trials) Regulations 2004. PROTOCOL WAIVERS ARE NOT PERMITTED.

4.3 Effective Methods of Contraception

To be eligible for the trial, female patients of child-bearing potential who are sexually active must confirm that they understand the need to use a highly effective method of contraception from 1 month prior to enrolling in the trial until the end of their trial participation. Female patients of child-bearing potential must also confirm they understand that their male partner should use an effective method of contraception for the duration of any ECP treatment. Highly effective methods include:

Female participants	Male partners of female participants
• Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal) • progesterone-only hormonal contraceptive associated with inhibition of ovulation (oral, injectable, implantable) • intrauterine device (IUD) • intrauterine hormone-releasing system (IUS) • bilateral tube occlusion or hysterectomy • vasectomised partner (>3 months earlier) • sexual abstinence	• Condom • Sexual abstinence • Vasectomy

Fertile male patients with female partners of child-bearing potential must confirm they understand the need to use a barrier method of contraception from randomisation into the trial up until the end of any ECP treatment. They must also confirm they understand that their female partner should use

an effective method of contraception from the time of first ECP treatment until end of their trial participation as detailed below:

Male participants	Female partners of male participants
• Condom • Sexual abstinence • Vasectomy	• Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal) • progesterone-only hormonal contraceptive associated with inhibition of ovulation (oral, injectable, implantable) • intrauterine device (IUD) • intrauterine hormone-releasing system (IUS) • bilateral tube occlusion or hysterectomy • vasectomised partner (>3 months earlier) • sexual abstinence

Details about applicable contraceptive methods explained to participants should be recorded in the participant's medical record. For both male and female patients, the practice of sexual abstinence must be in line with preferred and usual lifestyle and documented in the participant's medical record and eCRF. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not considered acceptable methods of highly effective contraception for the purposes of the trial.

Females who are amenorrheic for more than 12 months are considered not to be of child-bearing potential.

5. TRIAL PROCEDURES

5.1 Recruitment

5.1.1 Patient Identification

All adult lung transplant recipients remain under life-long follow up. This follow up is focused on maintaining the patient's overall wellbeing as well as carefully monitoring their lung allograft health. Alongside regular clinic visits, patients have direct access to their centres to be reviewed at short notice if they develop any new symptoms especially those suggesting their lung health may be affected, such as cough, sputum production, shortness of breath or chest infection. As a result, any fall in lung allograft function from baseline that suggests possible new onset CLAD or progression of previously diagnosed but stable CLAD is investigated promptly to identify and treat any non-CLAD causes. If no alternative cause is identified, or if the treatment of any non-CLAD causes fails to correct the fall in function, then all patients, who have not previously been treated with prolonged neomacrolide therapy, should receive a trial of azithromycin 250-500mg three times/week for at least 6 weeks. If the azithromycin, in this case given for anti-inflammatory rather than antibiotic properties, fails to show any effect and lung function continues to decline, then CLAD is confirmed and the patient may be eligible to participate in E-CLAD UK.

5.1.2 Pre-Screening for Study Participants: Recommendations

To ensure that all potentially eligible patients are approached in a timely manner, it is important that bilateral lung, or heart and bilateral lung transplantation patients with early and progressive CLAD are identified in pre-screening. This will enable a timely approach to potentially eligible participants. It is recommended that the following patients should be monitored in clinical practice as patients who may become potentially eligible:

1. Patients undergoing investigation for a new >10% fall in FEV1 where a potentially reversible is either not identified or is treated and response to treatment assessed.
2. Patients commencing a trial of long-term azithromycin therapy due to a drop in lung function
3. Patients with an FEV1 between 85-51% of personal best FEV1 value post-transplant (equivalent to New ISHLT CLAD Stages 1 and 2) with evidence of CLAD progression
4. Patients with an FEV1 >85% of personal best FEV1 associated with a ≥ 200 mL decrease in FEV1 in the previous 12 months.

These patients will not be formally approached at this time and no screening data will be collected on these patients; this is a recommendation for clinicians to pre-screen their caseload for future potential participants. These participants will only be formally screened and approached regarding potential participation in the trial once a new CLAD diagnosis, or progression of existing CLAD is suspected.

5.1.3 Screening

All patients aged 16 and over who have received a bilateral (single sequential) lung or heart and (bilateral) lung transplantation and completed a trial of azithromycin therapy for suspected CLAD will be screened for eligibility. Patients aged 16 and over with an existing diagnosis of CLAD who had previously stabilised but in whom lung function is declining due to potential progressive CLAD will also be screened for eligibility.

Patients who have previously responded to a course of azithromycin but went on to develop CLAD subsequently are still potentially eligible even if they are continuing longer term azithromycin for non-CLAD benefits.

An electronic screening log, integrated into the Sealed Envelope Redpill database will capture anonymised screening data including:

- The number of participants presenting with suspected CLAD and commenced/completed a course of azithromycin.
- Number of patients approached and provided with a PIS.
- The number of patients eligible/not eligible and reason (e.g. responded to azithromycin and CLAD excluded).
- Eligible patients approached for consent.
- Eligible patients not approached and the reasons why.
- Patients declined/not consented and the reasons why (if known).

5.1.4. Initial Approach

The initial approach to the patient regarding the trial will be by the treating clinician who will explain that they may be eligible to take part in a clinical trial. Potentially eligible patients will be provided with a short study participation information sheet (PIS) and an explanation of the purpose of the study and what it would involve. If having read this the participant is interested in receiving more information a copy of the full participation information sheet (PIS) will be provided. The patient will be advised to read the full information sheet carefully and discuss the trial with members of their family and/or GP if they feel this would be beneficial. The patients will be advised that they will be given the opportunity to ask any questions and discuss the trial and their eligibility in more detail at their next appointment. All patients will be given a minimum of 24 hours to consider participation to ensure they understand what the study involves and the risks for them.

5.1.5 Consent

When progressive CLAD is confirmed written informed consent must be obtained prior to any research assessments being carried out.

Formal written consent and confirmation of eligibility to participate in the trial will be taken by the site PI or delegated local Co-Investigator. The consent form will indicate consent to be approached to participate in the optional qualitative interview sub-study as well as the main study. Those who do not wish to take part in the qualitative sub-study will still be able to participate in the main trial.

Consent will also be sought for access to data generated during longer-term clinical follow up, this is also not mandatory for participation in the trial.

The original signed Consent Form will be filed in the Investigator Site File (ISF) and a copy filed in the patient clinical notes. Copies of the PIS used will also be filed in the ISF and clinical notes. Consent must be received prior to any trial specific assessments.

A copy of the completed consent form will also be sent by site to the secure NCTU email nctu.ECLAD.conf@nhs.net – this is for safety monitoring purposes. As this document contains patient identifiable information, an nhs.net account must be used to send this document. For sites that do not have nhs.net accounts, another secure method may be used but this must be discussed with and agreed by the NCTU Trial Manager(s) prior to use.

Confirmation of on-going consent to continue participating in the trial will be sought at the start of each follow-up visit and documented in the participant's medical notes.

Eligibility for the trial must be confirmed by a clinical member of the team who is delegated this task on the trial delegation log. An eligibility checklist must also be completed and signed by the member of the clinical team delegated to this task. The original eligibility checklist will be filed in the ISF and a copy will be filed in the participant's medical record. A copy of the completed eligibility checklist must also be sent by site to the secure NCTU email nctu.ECLAD.conf@nhs.net – again this is for safety monitoring purposes

5.2 Baseline Assessments & Data Collection

After written informed consent is obtained the baseline assessment and data collection will be carried out. See 5.6 for Schedule of Events.

5.2.1. Pregnancy test

Where indicated a urine dip stick test will be carried out at baseline only (see section 4.3). This should be carried out before any other baseline assessments and if positive the patient will be withdrawn from the trial, no further data will be collected and advice regarding pregnancy provided by the clinical team.

5.2.2 Safety blood tests

Safety bloods may identify a contraindication to ECP or values where the ECP treatment may require caution or modifications if the participant were to be randomised to the ECP arm.

- Urea and electrolytes
  - Caution in patients with low eGFR<30mL/min as will need to tolerate the fluid changes associated with ECP and will require closer monitoring.
  - Patients with end-stage renal disease who are dialysis dependent should not have haemodialysis performed on the same day as ECP treatment
- Liver Function Tests (LFTs)
  - High Bilirubin levels >3xUpper Limit of Normal may require adjustment of the Bowl optic sensor in the CELLEX ECP system
- Full Blood Count (FBC)
  - A total white cell count of >25 x10^9 per litre **is a contraindication to ECP**
  - A haematocrit <27% will require a large extra-cellular volume draw during ECP treatment and may cause haemodynamic instability. Blood transfusion prior to treatment or a blood prime at the time of ECP treatment will be required. A risk assessment of enrolling a participant with HCT <27% should be made by the PI considering all other co-morbidities.
  - A platelet count <20.0 × 10^9 per litre will require platelet transfusion and avoidance of heparin anticoagulation during ECP treatment.

If safety bloods indicate either a contraindication, caution or modification to ECP treatment, then the results and implications are to be discussed with the patient before deciding whether to continue in the study or not. The results of safety bloods must be shared by the research team with the ECP delivery team to ensure any additional requirements are implemented.

In the event that heparin is contraindicated during ECP treatment, then alternative suitable anticoagulants such as citrate may be used during the ECP process.

5.2.3 Routine Data Collection and Routine Clinical Assessment

The following routinely collected information and clinical assessments will be collected:

- Demographics:
  - Sex at birth.
  - Date of birth & current age.
  - Ethnicity.
- Relevant past medical history (PMH) and current treatment:
  - Details of history of disease.
  - Relevant PMH.
  - Current medical conditions (recorded to month/year of onset where possible).
  - Surgical interventions (previous and planned).
  - Any non-drug therapies.
- ISHLT CLAD stage and CLAD phenotype (definitions in section 7)
- Results of routine clinical assessments:
  - Most recent chest X-ray.
  - Most recent PFT Spirometry FEV1/FVC and values from the preceding 12weeks (minimum 2 readings obtained at least 3 weeks apart and at least 3 weeks prior to consent plus the baseline recordings)*.
  - Physical examination assessments.

* In the event that there are not at least 2 readings including the study baseline within the 12 week period preceding the baseline visit, then data can be collected up to 26 weeks prior to baseline visit. These will ideally have been collected at clinical appointments but home readings are acceptable.

5.2.4 Research Specific Assessment

The following research assessments will be carried out at baseline;

- Full Pulmonary Function Tests (PFT):
  - Spirometry comprising FEV1 and FVC.
  - Flow Volume Loop including FEF25-75
  - Static Lung volumes comprising Total Lung Capacity (TLC) and Residual Volume (RV).
  - Total diffusing capacity (DLCO), alveolar volume (Va) and volume corrected diffusing capacity (KCO).
  - Pulse oximetry at rest.
- Research blood samples
  - 1 x 6ml lithium heparin tube
  - 2 x 4ml serum tubes
  - 1 x 3ml RNA tube

(see section 5.4.4 and E-CLAD UK laboratory manual for processing and storage information)

- 6MWT

- To prevent any delays in initiating ECP (should the participant be randomised to that arm) assess suitability of venous access at baseline visit and determine if peripheral cannulation is possible or whether a central venous catheter may be required

5.2.5 Patient Reported Outcome Measures

- EQ-5D-5L questionnaire.
- SF-36 v2 questionnaire.

5.3 Randomisation

Following completion of baseline data collection, participants confirmed as eligible for the trial will be randomised by a delegated and trained member of the research team.

5.3.1 Randomisation details

Participants will be randomised to receive either ECP plus SOC (treatment arm) for 24 weeks or SOC (control arm) alone. Two variables will be used to achieve a balanced allocation of participants between the two trial arms:

- Site
- CLAD phenotype – RAS / BOS / mixed (For definitions see section 7)

Stratified block randomisation, targeting 1:1 allocation to the two trial arms, will be used. The trial is not blinded and so no arrangements will be required for unblinding.

5.3.2 Randomisation System

Randomisation will be carried out by a delegated and trained member of the research team at each site using Sealed Envelope's randomisation system which is, a central, secure, 24-hour web-based randomisation system integrated into the Red Pill database.

Randomisation system web address:
https://www.sealedenvelope.com/access/
The system is available 24 hours a day, 7 days a week

This should be done during the patient's baseline visit in order to simplify arrangement of an initial ECP visit if patient randomised into this arm.

In the event that the online randomisation system is not accessible, the site team should contact the NCTU data management team within normal working hours (9am – 5pm Monday to Friday, excluding bank holidays and Newcastle University closures):

E-mail: nctu.database.support@newcastle.ac.uk

5.3.3 Blinding

This trial is unblinded. Study participants, clinicians and the NCTU team will be aware of treatment allocation. The Statistical Analysis Plan (SAP) will be developed by statisticians who are unaware of

treatment allocation and will be finalised and signed-off prior to unblinded data being reviewed by the DMC. The SAP will contain full details of the final analyses, with details of who will perform these analyses. Trial statisticians will have access to unblinded data for the purposes of creating DMC reports. No other members of the research team will have access to the unblinded data contained in closed DMC reports, unless the DMC request that unblinded information is released. In the case that a major amendment is proposed to the SAP, this will be approved by an appropriate blinded independent statistician (the independent Trial Steering Committee statistician or an appropriate senior member of the Biostatistics Research Group).

5.4 Follow up assessments and Data Collection

5.4.1 Schedule of Events

		Week 0**		Week 2 +/- 7 days	Week 4 +/- 7 days	Week 6 +/- 7 days	Week 8 +/- 7 days	Week 10 +/- 7 days	Week 12 +/- 7 days	Week 16 +/- 7 days	Week 20 +/- 7 days	Week 24 +/- 7 days ****	
Activity	Screening at clinical assessments	Baseline Visit	ECP only* (0-14 days)	ECP only	Research Assessment	ECP only	Research Assessment	ECP only	Research Assessment	Research Assessment	Research Assessment	Research Assessment	
Screening													
Screen medical notes	x												
Provide PIS	x												
Initial Eligibility check	x												
Consent													
Informed Consent		x											
Confirmation of eligibility		x											
Pregnancy Test		x											
Randomisation		x											
Safety Bloods (FBC, U&E, LFT)		x											
Routine Data Collection													
Demographics		x											
PMH		x											
Clinical/physical assessment		x			x		X		x	x	x	x	
Routine blood tests***					x		X		x	x	x	x	
Chest X-ray findings		x			x		X		x	x	x	x	
Medication review		x			x		X		x	x	x	x	
PFT Spirometry (FEV/FVC)		x			x		x		x	x	x	x	
Survival status												x	
Research assessments													
Research Bloods		x							x			x	
6 MWT		x										x	
EQ-5D-5L		x										x	
SF-36 v2		x										x	
ISHLT CLAD score		x										x	
Research full PFT		x										x	
AE & SAE Reporting			x	x	x	x	x	x	x	x	x	x	
Assessment of Response									X*****				
Assess if cannula possible or catheter required		x											
ECP arm only													
ECP Cycle (2 days) + clinical bloods			1	2	3	4	5	6	7	8	9		
∞Pre and post ECP (NCL only) (2 x 20mls)			x						x		x		

*The first ECP cycle should ideally take place within 14 days of randomisation.
If ECP cycle 1 is >28 days after randomisation this should be documented as a deviation
If ECP cycle 1 is >14 days after randomisation then baseline Spirometry should be repeated
****Visit window extended to +30 days if participant believed to have treatable non-CLAD condition at time of planned visit

**Follow up assessments are from date of randomisation in control arm, and from date of commencing ECP for intervention arm.
*** Routine Blood Tests – Full Blood Count, Urea and Electrolytes and Liver Function tests
***** For those in the ECP arm participants must have received 6 treatment cycles prior to the formal 12 week assessment of response taking place – see sections 5.4.5 and 5.5.1 for details
∞ Pre and Post ECP research Blood for apoptosis assay in Newcastle participants only for mechanistic sub study

5.4.2 Follow up Assessment time points for all participants

Follow up assessments will take place at 4, 8, 12, 16, 20 and 24 weeks (see Schedule of Events in section 5.4.1). For participants in the SOC arm week 0 will be baseline assessment. For participants in the ECP arm week 0 will be from the day the first ECP treatment is commenced. At the 12-week assessment all participants will be reviewed to identify non-responders in both groups (see section 5.5).

Follow up visits should align with routine clinical appointments where possible. Visit windows have been incorporated into the schedule of events (see section 5.4.1) to enable assessments and collection of routine data in line with the regular clinical visits already attended.

5.4.3 Routine Data Collection for all participants

The following routinely collected information will be collected **at each assessment** time point (4, 8, 12, 16, 20 and 24 weeks):

- Changes to CLAD related symptoms.
- Changes to medication or non-drug therapy.
- Changes to routine clinical care.
- Any changes in treatment or new surgical interventions.
- Change in ISHLT CLAD stage.
- Additional clinic visits, urgent and unscheduled clinical assessments, or hospital admissions since previous assessment

The following routine clinical assessment results will be collected (preferably day of assessment):

- Most recent routine bloods (FBC, U&E's, LFT's).
- Most recent chest X-ray.
- Most recent PFT spirometry FEV1/FVC.
- Physical assessments.

5.4.4 Research Blood Samples for all participants

The following research bloods samples, will be taken from all participants at study baseline, 12 and 24 weeks for mechanistic analysis and evaluation of immune response

- 1 x 6ml lithium heparin tube
- 2 x 4ml serum tubes
- 1 x 3ml RNA tube

Processing of blood samples at site

- 1 x 6ml lithium heparin tube
    - This sample will be used for immunophenotyping. Immediately after collection the blood tube should be mixed well by inverting 8-10 times.
    - Sample can be kept at room temperature prior to shipping
    - Sample should be shipped on the day of collection (see E-CLAD UK laboratory manual for details)

- 2 x 4ml serum tubes
    - These samples will be used for immune marker analysis
    - Samples should be left at room temperature for 30-60 mins before processing

- Processed samples should be stored in -80°C freezer then batch shipped (see E-CLAD UK laboratory manual for details)
- Any sample remaining after the separation of serum should be disposed of in accordance with local policy.

- 1 x 3ml RNA tube
  - This sample will be used for transcriptomics
  - After collection, the blood tube should be mixed well by shaking or briefly vortexing contents
  - Samples should be stored in -80°C freezer then batch shipped (see E-CLAD UK laboratory manual for details)

The research blood samples will be analysed by a central laboratory at either Newcastle University or a commercial laboratory called Melio Health.

The samples going to Melio Health (those in the lithium heparin tubes) must be received by them the day following collection (ideally within 24 hours of collection). As Melio Health is only able to accept samples Monday-Friday, this means that these samples will need to be collected Monday to Thursday. Royal Mail safe boxes will be used to send these samples using overnight next day delivery. Sites must ensure that they know what time the last post collection is from their hospital post room and ensure samples are at the post room in time for the last post. This may mean that a morning appointment for the baseline, 12 week and 24 week visit will be necessary.

For participants receiving ECP, these bloods should be taken prior to commencing the treatment cycle that coincides with the visit where research bloods are due. There should be a minimum of 10 days between the previous cycle of ECP finishing and the 12 week research bloods being collected.

The week 12 research blood sample is to be collected even if the patient is classed as a non-responder following the 12 week assessment of response.

For full details about how all bloods must be collected, processed, labelled and packaged, see the blood sample section of the E-CLAD-UK laboratory manual.

5.4.5 12 Week Assessment of Response

All participants will be reviewed at 12 weeks to assess response and identify non-responders in both groups. Response will be determined by the % change in the FEV1 or FVC compared to baseline measurements obtained from routinely collected PFT Spirometry data (see 5.5 for identification of non-responders).

It is important to distinguish if a decline in FEV1 or FVC is due to progressive CLAD or potentially a non CLAD cause (see section 5.5).

For participants allocated to ECP treatment, the 12 week assessment of response must be completed and the decision made to continue treatment before a participant receives their 7th cycle of ECP treatment. This assessment should take place on the same day as the scheduled ECP treatment or as close to as possible.

If a participant receiving ECP is identified as a non-responder due to progressive CLAD, ECP may be continued if it is felt by the PI to be of clinical benefit, whilst alternative rescue therapies are being arranged if appropriate. See section 5.5.1 for additional details.

Please note: for participants in the ECP arm, 6 treatment cycles must have been received prior to the 12 week assessment of response taking place (see section 5.5.1). This may mean the 12 week assessment of response taking place later than 12 weeks if previous ECP treatments have been delivered towards the end of the visit windows outlined in the schedule of events. If the assessment still takes place within the protocol window (i.e. 12 weeks +/- 7 days) this is fine, if the assessment takes place outside of this window (i.e. from weeks 13 onwards) this would need to be recorded on the site deviation log.

5.5 Identification of Non-Responders

As E-CLAD UK is an intervention study with an efficacy endpoint, it is very important that every possible effort is made to allow participants to safely complete the study as *per protocol*. The aim of this study is to determine if ECP is efficacious in stabilising CLAD and therefore it is critical that sufficient ECP treatment is given to participants in the treatment arm to perform this assessment. All participants will be assessed at 12 weeks to assess response and identify non-responders in both groups.

If there is a >20% fall in FEV1 or FVC from baseline either within or at the 12-week assessment, then it is important for site PIs to confirm if this is due to progressive CLAD and not an intercurrent infection, new or progressive large airway obstruction or an extra-pulmonary cause. Participants can only be identified as a non-responder when a >20% fall in FEV1 or FVC is confirmed as being due to progressive CLAD. If there is any doubt that the >20% fall in FEV1 or FVC is due to progressive CLAD, then the participant should remain in the study and possible other causes should be fully treated and lung function reassessed at a suitable interval not exceeding the next study visit.

For any participants where CLAD progression means further rescue treatment is required which is not standard of care for patients suffering from CLAD (for example TLI), it is important to note that these participants must be withdrawn from the E-CLAD UK trial prior to any rescue treatment being given.

A decision Tree is provided in Appendix 6 regarding identifying non-responders and whether they are able to continue in the trial depending on their circumstances.

5.5.1 Participants in the ECP + SOC arm

At 12 weeks participants will be reviewed to assess response to treatment. Participants will have received 6 of the total 9 cycles of ECP planned in the treatment arm. Six cycles of ECP provides a meaningful treatment exposure and furthermore allows time for identification of participants who have rapidly progressive CLAD disease despite receiving an intensive short course of ECP therapy.

If at 12 weeks, either FEV1 or FVC has >20% decline from baseline measurements at trial entry due to progressive CLAD, they will be deemed non-responders to ECP plus SOC due to an insufficient therapeutic effect.

If a participant in the ECP plus SOC arm has a >20% fall in FEV1 or FVC from study baseline before their 12 week study visit and this is confirmed to be due to very rapidly progressive CLAD, then the site PI should assess the balance of risks in continuing with ECP treatment until 6 cycles have been completed or declaring the patient a non-responder before a meaningful exposure to ECP therapy has been achieved.

None of the potential rescue therapies that could be offered to participants discontinuing ECP therapy in the study have proven efficacy in treatment of CLAD in clinical trials and so this should be factored in any decision making by the site PI in identifying a participant as a non-responder before their 12 weeks study visit. A potential approach in those with a >20% fall in FEV1 or FVC before 12 weeks is to

prepare for access to a rescue treatment while also continuing to deliver ECP in the study so that this can commence promptly after the 12 weeks study visit.

In such situations, it is recommended that the site PI discusses the circumstances with the study CI to help ensure consistency of approach across centres in such cases.

Participants in the Newcastle mechanistic sub-study cohort who are classified as a non-responder at the 12 week assessment should still have their pre-ECP research blood sample collected even if they do not go on and have a 7th cycle of ECP treatment. This is to allow comparison with the baseline sample.

5.5.2 Participants in the SOC arm

If at 12 weeks, either FEV1 or FVC has >20% decline from baseline measurements at trial entry due to progressive CLAD, they will be deemed non-responders to SOC.

If a participant in the SOC arm has a >20% fall in FEV1 or FVC from study baseline before their 12 week study visit and this is confirmed to be due to very rapidly progressive CLAD, then the site PI should assess the balance of risks in continuing with SOC or consider introducing a rescue treatment outside the trial.

In such situations, it is recommended that the site PI discusses the circumstances with the study CI to help ensure consistency of approach across centres in such cases.

5.5.3 Primary endpoint and treatments for non-responders

Non-responders will be censored and included as 'non-stabilised' in the primary endpoint analysis. Non-responders will be eligible for rescue treatment outside the study. If rescue treatment will be given the participant must be withdrawn fully from the trial at the point that the rescue treatment commences. Use of any rescue treatment is at the discretion of the usual treating lung transplant physician.

5.6 Final Assessment for all participants

Routine clinical data should be assessed prior to commencing research specific assessments at the final assessment schedule for week 24. If the participant has seen a drop in lung function that is believed to be non-CLAD related and reversible, then the final assessment should be rearranged to allow any treatment to take place. The rearranged visit can be up to, but no later than, 30 days after the 24 week date. Unless cancelled for non-CLAD reasons as outlined above, the week 24 visit should take place at 24 weeks +/- 7 days.

The following research specific assessments will be repeated at the final assessment at 24 weeks:

- Full Pulmonary Function Tests (PFT):
  - Spirometry comprising FEV1 and FVC.
  - Flow Volume Loop including FEF25-75
  - Static Lung volumes comprising Total Lung Capacity (TLC) and Residual Volume (RV).
  - Total diffusing capacity (DLCO), alveolar volume (Va) and volume corrected diffusing capacity (KCO).
  - Pulse oximetry at rest.
- 6 MWT
- EQ-5D-5L questionnaire
- SF-36 v2 questionnaire

Where a participant is withdrawn from the study before the final assessment, the final assessment should be carried out as close to the time of withdrawal with the participant's permission.

See withdrawal section 5.12 for further details.

5.7 Additional information and data collection at ECP visits

Participants allocated to receive ECP will attend their respective ECP unit for treatment at 0, 2, 4, 6, 8, 10, 12, 16, 20 weeks. At weeks 4, 8, 12, 16, 20 and 24, data regarding the patient's condition, lung function and changes to CLAD treatment will also be collected and recorded in the eCRF. Where the ECP treatment visit aligns with the follow up assessments (4, 8, 12, and 20 weeks), the research assessments should take place prior to the ECP treatment commencing.

Ideally sites should try to adhere to 14 days between ECP treatment cycles wherever possible. for cycles 1-7 and 28 days for cycles 8 and 9. Where this is not possible there should be a minimum of 10 days between ECP treatment cycles. and a maximum of 21 days between ECP treatment cycles.

The clinical assessments and blood samples taken at the ECP treatment visits are for clinical purposes to ensure it is safe to proceed with treatment and should take place prior to commencing the ECP treatment cycle as per usual clinical practice, matching those normally performed at each ECP unit. Any results necessitating alterations to the standard ECP protocol or deferment of treatment are to be recorded in the eCRF. There are no additional research assessments to be undertaken at each ECP treatment visit.

AE and SAE reporting and concomitant medication review should coincide with each trial visit. For weeks 2, 6 and 10 where patients receive ECP treatment but are not required for routine clinical assessment, details may be collected by the research team via a telephone call to the patient. For information on reporting AEs and SAEs, including those identified during the ECP procedure see section 8.2.

All participants in the ECP arm must be followed up for a minimum of 4 weeks after the last ECP treatment and any adverse events noted during this time reported as per section 9.

A data card comes as standard with each ECP treatment kit. This is inserted into the machine and collects data about the machine settings and the way the treatment went. For participants in the E-CLAD UK trial we are asking ECP teams to follow the steps below:

1. Record the ID of the ECP treatment kit on the participants treatment record – this links the participant to the kit that was used to treat them and the card that will contain the treatment data.
2. The ECP specialist nurse delivering the treatment for an ECLAD-UK participant to enter 9999 into the operator ID box. This will allow the Therakos team to recognise the entry as an E-CLAD UK participant treatment.

This will allow the data from the data card to link back to the participant and will provide an additional safety net in case there were any adverse events associated with a treatment.

There is a UVA guidance document that should be handed out to participants randomised to the ECP arm. This provides participants with a reminder regarding sunglasses and sun cream requirements after ECP treatment. There is a trial safety card that must also be handed out to participants randomised to receive ECP to keep with them at all times during trial participation.

Therakos have also provided the trial with a supply of ECP starter packs that include key items such as sunglasses and sunscreen. These should be given to participants randomised to receive ECP. Each site

will be provided with a supply by NCTU. If possible it would therefore be beneficial for the research team to perform randomisation while the participant is still in attendance at the baseline visit, so that the starter pack and UVA guidance document can be provided straight away if required. If this is not possible then the packs/guidance document should be given to the participant at their next appointment and before they commence ECP.

5.8 Data collection if patient unable to attend visits

There may be situations where a patient is unable to attend for study visits, for example due to needing to isolate because of COVID-19. Wherever possible, this should be rearranged to another time within the visit window (please see section 5.4.1 Schedule of Events for details regarding visit windows). If this is not possible then the visit should be arranged to take place remotely with as many procedures completed as possible. This should include spirometry where the patient has access to suitable equipment at home and is required for a study visit. Home recorded FEV1 and FVC values should not be used as definitive readings for classifying non-responders.

The week 12 assessment of response visit must take place in clinic and cannot be completed remotely. If a patient is unable to attend a planned week 12 visit then it should be rearranged to another time within the visit window. If this is not possible then it should take place as soon as possible outside the window and reported as a deviation.

5.10 Payments to Participants

The research team at each site will support lung transplant recipients taking part in the study. All the participants will be well known to their local clinical team, the site PI, and most Co-Investigators as they will be under regular follow up at the centre. No payments or rewards are being provided to patients for participating in the trial itself, but the trial will provide an allowance for expenses associated with participation. Due to the intensive schedule of visits, especially in the ECP treatment arm, and the distances that many lung transplant recipients live from their transplant centre, we will support a contribution to travel and accommodation costs for them and an accompanying carer where appropriate. A tailored approach to travel and accommodation support will be taken, depending on travel distances and ease of commuting and if they have their own transport available which is a preferred route for most to attend for treatment. Costs will only be provided as part of the study when the visit is entirely study related as several of the study activities will coincide with scheduled clinic visits, which the patients would be making anyway.

5.11 Discontinuation of Allocated Trial Treatment

Participants have the right to discontinue their allocated trial treatment at any time. The participant is not required to provide a reason; however, they will be encouraged to do so to ensure that information relevant to the trial design, medication / intervention tolerability and efficacy is collected where possible. A Discontinuation of Trial Treatment Form needs to be completed and any reason provided should be documented in both the electronic case report form (eCRF) and the participant's medical records.

All participants choosing to discontinue ECP treatment / SOC treatment for reasons other than disease progression (for example personal choice) should be encouraged to continue with the remaining trial visits and assessments. The investigator/treating clinician will discuss with the participant which remaining trial visits are required and if the participant finds this acceptable to continue with the visits.

Following cessation of ECP treatment / SOC treatment, the participant's treatment regimen will be decided by the investigator/treating clinician as per routine care.

Please note: If the participant starts another rescue therapy that is not part of usual standard of care (for example TLI) they will then need to be withdrawn from the trial and no further trial visits will occur once this rescue therapy has started, however the patient will be asked to allow the use of routinely collected data until the end of the trial follow up period.

5.12 Withdrawal from Trial

Either the participant or the treating clinician may make the decision to withdraw the patient from the trial. Discontinuation of allocated trial ECP treatment or SOC treatment is not necessarily a withdrawal from the trial if the participant is willing to continue with trial visits where this is an option (see section 5.11). **Please note:** where trial treatment is being stopped due to non-response and need for rescue treatment, the participant must be fully withdrawn from the trial. Please see appendix 5 for non-responder decision tree.

If the participant is withdrawn from the trial, they cannot continue with ECP treatment and will be followed up for adverse event reporting purposes only for an additional 4 weeks from the point of stopping ECP. With participant consent, the week 24 research activities (see section 5.6) should be undertaken at the last study visit before withdrawal. If the participant is withdrawn after the baseline visit and before the week 12 visit then, with consent, the week 12 research blood samples should be collected at the last study visit before withdrawal. If the participant is withdrawn after the week 12 visit, then no further research blood samples are required.

All withdrawals from the trial should be asked if they allow the use of routinely collected data for the remainder of the trial follow up period

If the patient requests to withdraw from the mechanistic sub-study or qualitative sub-study, they can still remain in the main trial.

5.12.1. Participant Requested Withdrawal from the trial

Participants have the right to fully withdraw from the trial at any time without having to give a reason. When a participant states they want to withdraw from the trial, sites should try to ascertain the reason for withdrawal and document this reason within the withdrawal form eCRF and participant's medical records.

Where a participant withdraws consent, no further research assessments will take place and the participant should be asked if they will allow the use of routinely collected data until the end of the trial follow up period. Data collected up to the point of withdrawal will be retained and included in the analyses. The participant's decision to allow the use of routinely collected data or not should be clearly documented.

5.12.2. Investigator Led Withdrawal from the trial

The investigator/treating clinician may withdraw a participant from the trial at any time if they deem it necessary for the following reasons:

- Continuing to attend trial visits and undergoing trial assessments would place unreasonable demands on the physical or psychological health of the participant. If participant and investigator agree, any assessments occurring as part of routine care would also be recorded in the eCRF.

- The participant loses capacity for a prolonged period.
- An adverse event, which results in inability to continue to comply with trial procedures.
- Inability to secure appropriate vascular access for ECP treatment to be delivered to participant in the ECP+SOC arm.
- Pregnancy.
- Significant protocol deviation or non-compliance.
- Termination of the clinical trial by the Sponsor.

Where the decision is taken by the clinician to fully withdraw the participant from the trial, the following procedures will apply:

- If the participant has not yet received any ECP treatment, the participant should not participate in any further trial-related procedures.
- If the participant has received any ECP treatment including IMP administration as part of the process, the ECP treatment should be stopped, and followed up for adverse event reporting purposes only for an additional 4 weeks.

Information that a participant has received ECP treatment even if incorrectly enrolled/randomised must be documented in the eCRF.

5.12.3 Replacement of withdrawn participants

Participants who withdraw from the trial will be replaced in certain circumstances, and each case will be assessed individually.

A participant who is withdrawn in any of the following situations may be replaced:

- The participant is withdrawn from the trial prior to attending the next visit following their baseline assessment.
- The participant is found to be pregnant during the baseline assessment.
- The safety bloods taken at baseline show that the participant is ineligible for the trial.

5.13 End of Trial

The end of the clinical trial is defined as the final participant's 24-week follow-up visit being completed and all blood samples analysis for the final visits being completed. All data queries will be resolved, as far as possible, before the database is locked. The Sponsor, CI and the TSC have the right at any time to terminate the trial for clinical or administrative reasons.

The end of the trial will be reported to the Sponsor, Research Ethics Committee (REC), Regulatory Authority (RA) and NHS R&D Office(s) within 90 days, or 15 days if the study is terminated prematurely. It is the CI's responsibility to ensure that any appropriate follow-up is arranged for all participants; this will be delegated to the site PIs.

A final report will be provided to the Sponsor, REC, MHRA and Funder within one year of the end of the study.

Subject to funding a substantial amendment may be submitted to cover longer term follow of participants.

6. SUB-STUDIES PROCEDURES

6.1 Mechanistic sub-study

In additional to the research bloods collected for all participants, a subset of patients will be asked to consent to provide additional blood samples

6.1.1 Newcastle Mechanistic Cohort

Participants from the Newcastle site only who are enrolled in the ECP+SOC arm will be invited to provide additional blood samples immediately pre and post treatment cycle of ECP on 3 occasions. This will allow for analysis of immune tolerance and apoptotic cells throughout ECP treatment.

During the recruitment process for the main trial, participants from this site will be asked to consent to participate in this additional research blood sampling.

The following research bloods sample, will be taken immediately before ECP on day 1 and immediately after ECP on day 2 of ECP treatment cycles 1, 7 and 9 (week 0, 12 and 20).

- 20ml of whole blood in two EDTA tubes before ECP on day 1
- 20ml of whole blood in two EDTA tubes after ECP on day 2

Processing of blood samples at site:

- Tubes should be mixed immediately after collection by gentle inversion 8-10 times.
- Samples should be stored between 2-5 C in a fridge
- The laboratory staff should be contacted to arrange immediate collection

Note: Where possible please notify the laboratory staff prior to the sample collection to allow for immediate collection and transfer to the processing laboratory at Newcastle University.

6.1.2 Mechanistic Outcome Measures

Research blood samples will be collected for molecular and cellular analysis of peripheral blood during the study. The outcome measures are as follows:

i) The serum concentration of key immune markers including pro-inflammatory and anti-inflammatory cytokines, chemokines, and growth factors.
ii) The number, % and phenotype of circulating lymphocytes, monocytes, and dendritic cells detectable in blood.
iii) Transcriptional assessment of genes encoding effector molecules and immunosuppressive cytokines in leucocytes including T-lymphocytes.
iv) The % of circulating dendritic cells exhibiting a tolerogenic phenotype with reduced expression of co-stimulatory molecules in pre and post ECP samples.
v) The number, % and suppressive capacity of regulatory T-cells in pre and post ECP samples.

6.1.3 Storage and Analysis of Research Blood Samples

Please see the E-CLAD UK laboratory manual for further details about the storage, labelling and shipping of all research bloods.

It is the responsibility of the trial site to ensure that samples are appropriately labelled in accordance with the trial procedures to comply with the applicable legislation UK Data Protection Act 2018 and the UK GDPR as amended on 01 January 2021 by regulations under the European Union (Withdrawal) Act 2018, to reflect the UK's status outside the EU. Biological samples collected from participants as

part of this trial will be transported, stored, accessed, and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and 2006 Human Tissue (Scotland) Act.

All shipments of biological samples will be labelled and shipped according to local legislation.

A full chain of custody is maintained for all samples throughout their lifecycle. Please refer to the E-CLAD UK Laboratory Manual for further details.

The site is responsible for keeping full traceability of biological samples from the time the samples are collected from the participant, whilst in storage at the site until shipment. The site also needs to keep documentation to confirm receipt of samples shipped to analytical laboratories.

The sample receiver (analytical laboratory) is responsible for keeping full traceability of the samples received, whilst in their storage and during use until analysed, shipped, or disposed of.

The samples will be used up or disposed of after analyses or retained for further use as described below.

The sponsor keeps oversight of the entire sample life cycle through monitoring of the trial sites and analytical laboratories.

6.2 Qualitative Interview sub-study

A 24-month sub-study will involve up to 30 participants who consent to individual semi-structured interviews conducted by an experienced qualitative research associate. The purpose of these interviews is to understand patient perceptions, acceptability, and experiences of living with CLAD and of experiencing ECP therapy. This sub-study format is guided by the patient and public involvement (PPI) group consulted for this trial. Twenty participants in this sub-study will have undergone ECP.

During the recruitment process for the main trial, participants from across all five trial sites will have been given the option to consent to being contacted about the qualitative sub-study. From this pool of positive responses, the qualitative research team will engage in a process of purposive sampling, aiming to achieve variation across the sample in terms of age, gender, location (e.g., distance from treatment centre), length of time living with and stage of CLAD. Pseudonymised health data from the trial database will be provided to the qualitative research team. These categories are likely to have an impact on participants' experiences and were informed by consultation with the PPI panel. Any participants not selected for interview will be provided with a 'Thank you for volunteering' letter which will be distributed by sites. The qualitative research team will advise sites of participants not selected for interview.

Prior to contacting those who expressed an interest in participating in the qualitative interview sub-study, the team will check with site PIs or co-PIs as to the health status of the participant to ensure contact is appropriate. Selected participants will be provided with the qualitative sub-study PIS via email, post or at their next suitable study visit by the research team at sites. The qualitative sub-study PIS will provide potential participants with the option to contact the qualitative research team themselves if they wish, for further information or to express their decision to participate or not. Alternatively they can choose to wait for the qualitative research team to contact them. The qualitative team will respond via email or telephone to those participants that contact them about the interviews. Those who no longer wish to participate will not be contacted about the qualitative sub-study again. Those who wish to consider participation will be given time (approximately a week) to consider the information before being contacted by the qualitative team. Some participants may wish to arrange a time for an interview during the initial contact with the qualitative researcher and

this will be accommodated. The researcher will confirm that the PIS has been read, considered and understood, and that they still wish to participate prior to formal data collection commencing. Participants will be given the opportunity to ask questions prior to providing consent. Consent for the qualitative interview sub-study will be collected remotely. Participants may wish for a family member, friend, or carer to be present during the interview. Such requests will be accommodated, and the third party provided with an information sheet and consented prior to the interview commencing.

Participants will be interviewed in their own home, either by Zoom, Skype (or similar web-based technologies) or by telephone. This will allow greater inclusivity of participants and reduce travel time. Interviews will take place any time before a participant's 24 week follow up. This will allow the capture of patient experience at a range of different time scales. All interviews will be audio-recorded and transcribed verbatim.

As there will be a lag between participants initially consenting to the main study (and indicating at that stage if they would like to take part in an interview) and the interviews being conducted, a qualitative withdrawal form is available for any participants that subsequently change their mind. If a participant indicates to their research team that they no longer wish to take part in an interview, this withdrawal form should be completed, and the central trial management team informed of this so that the participant is not contacted any further regarding an interview.

Those who do not wish to take part in a structured interview in the sub-study will still be able to participate in the main study. Those who do participate will be able to withdraw from the qualitative interview sub-study at any time, without giving a reason. This will not impact their involvement in the main trial.

6.3 Health Economic Sub-study

A health economic evaluation will be undertaken at the end of the trial. No additional assessments will be performed by the patient as all data regarding patient treatment, interventions and hospitalisations are already collected in the ECRFs throughout the participant's involvement in the trial.

7. DEFINITIONS

CLAD is to be defined in line with the 2019 consensus report from the Pulmonary Council of the ISHLT (3).

7.1 Stages of CLAD

Stage	Spirometry
CLAD 0	Current FEV1 > 80% FEV1 baseline*
CLAD 1	Current FEV1 > 65 - 80% FEV1 baseline*
CLAD 2	Current FEV1 > 50 - 65% FEV1 baseline*
CLAD 3	Current FEV1 > 35 - 50% FEV1 baseline*
CLAD 4	Current FEV1 < 35% FEV1 baseline*

*Baseline defined as average of the two best post-operative FEV1 measured ≥3 weeks apart

7.2 Phenotypes of CLAD

7.2.1 Bronchiolitis Obliterans Syndrome (BOS):

1. Persistent ≥20% decline in FEV1 compared to best-achieved baseline~
2. Obstructive spirometry with FEV1/FVC <0.7
3. Absence of persistent pulmonary opacities on chest imaging (chest X-ray and/or computed tomography).

~ defined as average of the two best post-operative FEV1 measured ≥3 weeks apart

7.2.2 Restrictive Allograft Syndrome (RAS)

1. Persistent ≥20% decline in FEV1 (+/- FVC) compared to “best-achieved” baseline
2. Decrease ≥10% in total lung capacity (TLC) compared with “best-achieved” baseline*
3. Persistent opacities on chest imaging (chest X-ray and/or computed tomography)

*defined as the average of the two best TLC measurements obtained at the same time as or very near to the best 2 post-operative FEV1 measurements. In the absence of best-achieved TLC measurements, a decline of FVC of ≥20% compared to baseline can be used as a surrogate for restriction if additionally, Spirometry shows FEV1/FVC >0.7.

7.2.3 Mixed and Undefined CLAD Phenotypes

CLAD Phenotype	Obstruction	Restriction	CT Opacities
BOS	Yes	No	No
RAS	No	Yes	Yes
Mixed	Yes	Yes	Yes
Undefined	Yes	No	Yes
	Yes	Yes	No

Obstruction is defined by a fall in FEV1 (as described above) and associated with other indices of airflow limitation (FEV1/FVC ratio <0.70). Restriction is properly defined as a ≥10% reduction in baseline TLC. CT Opacities refers to parenchymal opacities and/or increasing pleural thickening consistent with a diagnosis of pulmonary and/or pleural fibrosis and likely to cause a restrictive physiology, rather than the airway-based changes consistent with bronchiectasis. Although opacities and bronchiectasis may coexist, in some cases, the presence of bronchiectasis may reflect traction changes on airways due to fibrotic parenchymal opacities.

Mixed phenotype exhibits elements of both BOS and RAS and, all cases that transition from a BOS phenotype to an RAS phenotype and vice-versa, will meet these criteria.

Undefined means definite CLAD, but with 2 possible combinations of variables, making it difficult to categorize in the upper panels (BOS, RAS, or mixed phenotype). For the purposes of Phenotype classification in the trial then Undefined will be combined with mixed in terms of randomisation.

7.3 Lung Function

Lung function stabilisation – defined as a less than or equal to a 10% loss in FEV1 and FVC from study baseline to 24 weeks.

Rapid decline – defined as a greater than 20% fall in FEV1 or FVC in the first 12 weeks from study baseline.

Non-responders – As outlined in the study flow chart in Section 3.3, a non-responder is defined as someone who experiences a decline in FEV1 or FVC of more than 10% at 24 weeks compared to baseline readings due to progressive CLAD. A non-responder may also be someone with a decline in FEV1 or FVC of >20% within 12 weeks of the baseline visit that is confirmed as being due to progressive CLAD.

8. TRIAL INTERVENTION

8.1 Description of Standard of Care

The management of lung transplant recipients both before and after the development of CLAD may vary subtly between the UK centres. However, the underlying principles are well aligned in terms of a standardised maintenance immunosuppression regime (cell cycle inhibitor, calcineurin inhibitor and corticosteroids) and prophylaxis against common viral, bacterial, and fungal infections with attention to blood pressure control, lipid profiles, preservation of renal function and bone protection. Acute cellular rejection of ISHLT grade A2 or higher is treated with short term augmentation of corticosteroids in all centres.

The diagnostic approach to new onset CLAD is also well aligned with the 2019 ISHLT criteria (3) with a diagnosis made only after a failed response to a trial of azithromycin therapy and exclusion of reversible causes such as cellular or humeral rejection, large airway anastomotic obstruction and infection. After a diagnosis of probable CLAD, patients are observed and those with progressive loss of lung function have traditionally been offered potential immunomodulatory therapy with either TLI or ECP depending on availability and funding. Other therapeutic approaches with little to no evidence to support them have generally been avoided. Retransplantation provides the only realistic therapeutic option in those who progress to very severe CLAD without significant other co-morbidities.

All five centres participating in this trial have agreed clear principles for the SOC for CLAD treatment. The basis remains supportive with supplementary oxygen for hypoxia, prevention and treatment of infective exacerbations, physical rehabilitation, and psychosocial support. This will be the approach in both arms of the study with use of ECP in the treatment arm the only difference.

Participants will not be treated with any immunomodulatory interventions such as TLI or ECP as part of SOC in the trial. Only if there is rapidly progressive CLAD disease by 12 weeks as defined in the

protocol (>20% decline in FEV1 or FVC) will the patient leave the study and be eligible to access immunomodulatory interventions outside the study at the discretion of the clinical team. If at any point after 12 weeks, but before 24 weeks, they reach >20% decline in FEV1 then they will also have the option to leave the study and access immunomodulatory treatments at the discretion of the clinical team.

For more details of the agreed Standard of Care Pathway for the trial, please see Appendix 1 of this protocol.

8.2. Description of ECP Treatment

ECP therapy is performed using the THERAKOS™ CELLEX™ Photopheresis System® which is an automated enclosed system which separates a given volume of the patient's whole blood into plasma, red blood cell and white blood cell fractions. The red cells and some of the plasma is immediately returned to the patient while the white cells and remaining plasma is collected in a separate chamber. This collection process is repeated over a number of cycles. The buffy coat suspension of white blood cells is then treated with the photosensitising drug methoxsalen. After the cells have absorbed this drug, they are exposed to UVA light radiation, and then returned back into the patient's body. THERAKOS™ have agreed to provide CELLEX™ System Procedural Kits at a discounted rate to sites for trial procedures. Sites are also able to loan a CELLEX™ system from THERAKOS™ if required to meet ECP capacity as a result of trial recruitment.

In this trial, UVADEX® (methoxsalen) Solution will be the investigational drug. UVADEX® (methoxsalen) Sterile Solution will be injected directly into the Recirculation Bag of the extracorporeal circuit after completion of the buffy coat collection, immediately prior to initiating photo-activation. The dose of UVADEX® used to inoculate these cells will be calculated based on the standard treatment volume formula (see section 8.6). Heparin is the standard anticoagulant for use with the THERAKOS™ CELLEX™ Photopheresis System®. However, sites may use other anticoagulants such as citrate if routinely used as part of their standard local ECP protocol or if heparin is contraindicated for a patient. Patients in the ECP arm should have all of their treatments with the THERAKOS™ CELLEX™ Photopheresis System® at a set frequency over the course of 24 weeks. Each treatment takes about 2-3 hours to complete, and each cycle consists of 2 treatments performed on consecutive days. The treatment schedule in the study protocol means patients randomised to the ECP arm must receive their first cycle ideally within 14 days of their baseline visit, but no later than 28 days after baseline visit. Cycles are then performed every 2 weeks for the first 12 weeks and then every 4 weeks for the next 12 weeks. By 24 weeks after the baseline visit those who complete the study will have received 9 cycles of ECP equating to 18 individual treatments.

8.2.1. Venous and Central Access for ECP treatment

IV access will be required for the administration of the ECP treatment via the THERAKOS™ CELLEX™ Photopheresis System. This should be provided in line with each sites' local procedures for the delivery of ECP treatment.

8.2.2. Peripheral Venous Catheters

If possible, it is preferable to administer the ECP treatment via peripheral venous access, to minimise the risk of infection. In single needle mode, the access device must be capable of withstanding the

negative pressures required to collect whole blood and the positive pressure used to return blood components.

In double needle mode, it may be possible to use a large gauge device for drawing and a smaller gauge device for return. It is recommended that more than one type of venous access device be available. Choose the one most suitable for the patient undergoing treatment.

For peripheral venepuncture, the following devices are suitable for peripheral access:

- 16G, 17G Fistula Needles DRAWING or RETURNING
- 17G, 18G IV Catheter (High durometer angiocatheter) drawing or returning
- 20G IV Catheter (High durometer angiocatheter) returning

8.2.3. Central Venous Catheters (CVC)

When peripheral venepuncture is not possible, alternative devices such as long-term indwelling catheters, temporary catheters, or subcutaneous ports may be used providing they meet the requirements below. Careful planning to ensure the appropriate device is implanted will prevent failed or shortened ECP therapies due to access failure.

Any catheter intended to be used with the THERAKOS™ CELLEX™ Photopheresis System must be able to withstand the negative pressure of the peristaltic pressure pumps without collapsing and they must provide a flow rate of at least 15 mL/min. Overall requirements are:

- Minimal internal diameter of 3.0 mm or 9FR. (1 mm = 3 French)
- Maximum length of 36 cm
- High durometer or stiffness of catheter (designed for haemodialysis or apheresis procedures to provide high flow output).

It may be necessary to replace a central venous catheter if it stops working or becomes blocked. This is at the discretion of the treating clinician and should be fully documented in the participant record, along with any impact that has on the ECP treatment, if appropriate.

Participants who have a CVC inserted to receive ECP therapy in the trial must be educated on the self-care requirements and signs of infection to look out for. Maintenance of CVC integrity such as exit site dressings and patency via regular flushes should be performed in line with local site policies.

8.2.4. Other access options

It may also be possible to administer the ECP via the THERAKOS™ CELLEX™ Photopheresis System using implanted venous access devices. However, please note that subcutaneous ports designed specifically for high-speed infusions will not provide adequate output for drawing. Implant only ports designed for both high-speed input and output are required.

The THERAKOS™ CELLEX™ Photopheresis System is also capable of both drawing from and returning to an AV Fistula or shunt. Centre-specific guidelines should be followed for accessing and maintaining the graft.

8.3. Name and Description of IMP

The participants in this trial will be randomised in a 1:1 ratio to receive either standard care plus UVADEX® (methoxsalen) solution as part of their ECP treatment, or standard care alone.

UVADEX® is clear, colourless to pale yellow solution, which is used for blood fraction modification. Each vial of UVADEX® contains 10ml of methoxsalen at a concentration of 20 micrograms/ml, giving a total of 200 micrograms per vial.

The other ingredients are Propylene Glycol, Ethanol 95%, Glacial Acetic Acid, Sodium Acetate Trihydrate, Sodium Hydroxide, Sodium Chloride and Water for Injections.

An SmPC will be used for the UVADEX® medication and should be referred to for further information.

8.4. Drug Storage and Supply

UVADEX® can be stored at room temperature but should not be stored at temperatures exceeding 25°C. No formal trial specific temperature monitoring will be required for the IMP. Standard hospital procedures for storing and managing medications will be followed.

UVADEX® will be prescribed by a suitably designated trial clinician and obtained via usual means from the hospital pharmacy or ward supplies for use on the ECP unit. Supplies should be obtained from standard NHS Hospital stock. No IMP will be provided by Sponsor. Used vials of UVADEX® solution will be destroyed locally following administration in accordance with local procedures. Accountability will be performed by the trial management team via collection of batch number, expiry date and dose given within the eCRFs.

8.5 Preparation and Labelling of IMP

Preparation of the UVADEX® prior to use with ECP is covered in section 8.6. There is no requirement for sites to label the product with Annex 13 compliant labels.

8.6 Dosage Schedule & Modifications

Participants randomised to ECP treatment will receive UVADEX® treatment up to 18 times (9 cycles) as part of the trial. The time points for the treatments are shown in the schedule of events in section 5.4.1. Each treatment will take place on two consecutive days.

During each photopheresis treatment, plasma and leukocyte enriched blood are obtained by centrifugation and collected into a photoactivation bag. The treatment volume (which is displayed on the display panel of the instrument) is then used to calculate the dose of UVADEX® required using the formula:

Treatment volume x 0.017 ml of UVADEX® for each treatment
For example: Treatment volume = 240 ml x 0.017 = 4.1 ml of UVADEX®

The dose of UVADEX® required will be different for each treatment for each participant.

The prescribed amount of UVADEX® will be calculated, as per the formula above, drawn from the single 10 ml vial and injected into the recirculation bag prior to the photoactivation phase. The leukocyte rich blood in the recirculation bag is then exposed to UVA light in a photoactivation chamber and re-infused into the participant. UVADEX® should be injected into the recirculation bag as soon as possible after withdrawing from the vial into a syringe to reduce the time the UVADEX® is in contact with the syringe. If the UVADEX® is exposed to a plastic syringe for longer than 1 hour it should be discarded.

8.7 Known Drug Reactions and Interactions

Methoxsalen has been shown to act primarily as a potent inhibitor of hepatic microsomal oxidative metabolic processes, including, but not limited to, CYP1A2, 2A6 and 2B1. Thus, it is to be expected that interactions will occur between methoxsalen and other medicinal products whose metabolism involves the hepatic cytochrome P450 system. The clearance of caffeine and antipyrine have been shown to be markedly reduced after methoxsalen treatment. Therefore, consumption of other P450 substrates may result in an extended half-life of methoxsalen, and consequently lead to prolonged photosensitivity and thus requiring continued precautions against exposure to sunlight beyond 24 hours following photopheresis treatment.

Studies have shown that methoxsalen also decreases the metabolic activation of paracetamol in animals and humans, probably because of methoxsalen-associated inhibition of hepatic cytochrome P450 oxidative transformation of paracetamol.

8.8 Concomitant Medications

All concomitant medications required for the standard care of the participants with CLAD will be allowed at the discretion of the investigator. A complete listing of all concomitant medication, including applicable contraceptive methods and vaccinations, received during the data collection period should be recorded in the eCRF and participant medical records. Concomitant use of methoxsalen and tolbutamide may lead to enhanced photosensitivity.

Special care should be exercised in treating patients who are receiving concomitant therapy (either topically or systemically) with known photosensitising agents. Such agents include fluoroquinolones, furosemide, nalidixic acid, phenothiazines, retinoids, sulphonamides, sulfonylureas, tetracyclines, thiazides and voriconazole or other azoles associated with photosensitivity.

8.9 Assessment of Compliance

Compliance with the ECP / IMP regimen will be recorded in the participant medical records and in the eCRF.

9. PHARMACOVIGILANCE

9.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward or unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions
Reference Safety Information (RSI)	The RSI is a list of medical terms detailing the ARs that are expected for an IMP and must be referred to when assessing a SAR for expectedness.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death • Is life-threatening* • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity • Consists of a congenital anomaly or birth defect • Other important medical events that jeopardise the participant or require intervention to prevent one of the above consequences *Life-threatening refers to an event in which the participant was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based upon the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the approved Reference Safety Information.

9.2 Recording and Reporting AEs and SAEs

Adverse Events:

All AEs occurring from the time of consent to end of trial participation, must be recorded in the AE eCRF page as well as the participant's medical notes.

Events which are due to the symptomatic deterioration of the participant, and which are expected for participants who have CLAD progression, do not need to be reported as AEs. These events will be recorded in the participant record and will be reported in the eCRF, but not as AEs.

All adverse events which are not associated with the deterioration of the participant or their non-response to treatment will be recorded as AEs, both for participants in the ECP treatment group and also for those in the SOC group. These events include the following:

- Transient fever
- Transient hypotension
- Dizziness / Pre-Syncope
- Nausea
- Vomiting
- Loss of appetite
- Headache
- Fatigue
- Minor photosensitivity reactions
- Local site infections associated with peripheral or central venous catheterisation
- Other Infections of all types: Bacterial Fungal Viral
- Worsening of any baseline medical condition eg hypertension, diabetes, gastro-oesophageal reflux
- Need for blood transfusion
- Need for platelet transfusion

This list is not exhaustive and any other AE which, in the opinion of the investigator is not due to the progression of CLAD, should be reported as an AE.

Serious Adverse Events and Serious Adverse Reactions:

All SAEs occurring from point of consent to end of trial participation (end of the last trial related assessment) must be reported to NCTU on an SAE form and recorded in the AE eCRF page and recorded as serious.

All SARs occurring from the time of first ECP treatment up until the last trial related assessment for the participant at week 24 must be reported to NCTU on an SAE form and also recorded in the AE eCRF page and recorded as serious. All participants in the ECP arm must be followed up for a minimum of 4 weeks after the last ECP treatment.

Following this defined active monitoring period for SARs, investigators are still required to report any SARs or SUSARs they become aware of for all trial participants for the duration of the study (i.e. up until LPLV).

An unscheduled hospitalisation, with any of the following causes, will need to be reported as an SAE:

- Systemic infection associated with central venous catheter use
- Systemic infections associated with peripheral cannulation
- Sepsis of any cause
- Pulmonary embolus
- Myocardial infarction
- Heart failure
- Renal failure new onset or significant deterioration of existing renal dysfunction needing renal replacement therapy
- Allergic reaction to Methoxsalen
- Severe photosensitivity reaction
- New onset cataracts
- New onset malignancy including skin malignancy
- Inability to secure suitable vascular access despite all reasonable attempts

This list is not exhaustive and any other SAE which, in the opinion of the investigator is not due to the progression of CLAD, should be reported as an SAE and an SAE form completed.

All SAEs/SARs must be reported to NCTU on an SAE Form and emailed to NCTU via secure email to the nctu.E-CLAD.sae@nhs.net circulation list as soon as possible and within **24 hours** of staff becoming aware of the event.

Preliminary reporting to NCTU via email or telephone is acceptable in order to meet the 24 hour reporting timeline, where circumstances do not allow for immediate completion of the SAE form. All initial SAE reporting must be reported on an initial SAE form and all subsequent information should be provided on the follow-up SAE form. However, the SAE form should be completed and submitted as soon as possible after the initial notification in order to comply with reporting timelines.

For sites where the ECP unit falls within a different trust to the research team, robust systems must be in place to ensure that any SAEs occurring during delivery of ECP treatment/while the participant is in the care of the ECP unit must be reported within these timescales to avoid deviations and allow for prompt onward reporting to regulatory bodies by sponsor if required.

The ECP team must ensure that the research team (including the PI) are notified of the SAE via email as soon as possible and within 24 hours of becoming aware. The central trial management team must also copied in to this email via nctu.E-CLAD.sae@nhs.net. This will ensure that the reporting timescales are met.

The research team will then commence completion of the SAE form with all information available at that time and send this to nctu.E-CLAD.sae@nhs.net as soon as possible.

For each SAE the following information will be collected:

- Full details in medical terms and case description.
- Event duration (start and end dates, if applicable).
- Action taken.
- Outcome.
- Seriousness criteria.
- Causality in the opinion of the chief investigator.

Any change of condition or other follow-up information should be submitted to NCTU at nctu.E-CLAD.sae@nhs.net as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

9.3 Reference Safety Information

The approved Reference Safety Information (RSI) is:

- Section 4.8 of the Uvadex 20 micrograms/ml Solution Summary of Product Characteristics (SmPC) dated 25/08/2021.

The SmPC is available via MHRA website: https://products.mhra.gov.uk/

9.4 Recording and Reporting SUSARs

All SARs or suspected SARs that occur during this trial must be reported by site to NCTU immediately (and no later than 24 hours of the site becoming aware of the event), through the provided SAE reporting method (see section 9.2). This will automatically be distributed to the Sponsor and CI.

The assessment of expectedness will be performed by the CI on behalf of Sponsor. Where the CI is unavailable, another medically qualified individual may be delegated this task via the trial delegation log. The assessment of expectedness will be performed against the approved RSI for the trial.

The RSI is contained within the Uvadex SmPC section 4.8 (see section 9.3 above)

All SUSARs must be reported to the MHRA and REC. Reporting to MHRA and REC will be performed by the trial Sponsor. This is reported using the electronic SUSAR form via the eSUSAR website. A copy of the electronic form and the CTIMP safety report will be sent to the REC in line with sponsor standard operating procedures.

Fatal and life-threatening SUSARs must be reported to the MHRA within 7 calendar days of notification (with a further 8 days for follow up information) by the Sponsor.

Non-life-threatening SUSARs must be reported to the MHRA by the Sponsor no later than 15 calendar days after notification with any relevant follow-up information sought and reported as soon as possible after the initial report.

NCTU will be responsible for ensuring that the CI undertakes the expectedness assessment to determine if a SAR is unexpected and requires reporting as a SUSAR. The reporting timeframe starts at day zero when the Sponsor is in receipt of a minimum set of information:

- Sponsor trial reference and trial name (sponsor reference).
- EudraCT number.
- Patient trial number
- Name of IMP(s).
- Date of notification of the event.
- Medical description of the event.
- Date of the onset of the event (including time of onset if available and event end date if applicable)
- Causality assessment.
- Seriousness of the event, particularly if life threatening or fatal.
- An identifiable reporter (e.g. PI).

The site is expected to fully cooperate with the NCTU in order that a full and detailed report can be submitted to the MHRA and REC within the required timelines.

Site PIs will be informed of all SUSARs by NCTU.

9.5 Protocol Specific Reporting Exclusions

Pre-planned hospitalisations (e.g. elective surgery) or scheduled treatment for pre-existing conditions that are not associated with clinical deterioration do not need to be reported as SAEs. Hospitalisations for administration of trial ECP therapy only will not be considered as SAEs.

9.6 Responsibilities

Principal Investigator or delegate

- Checking for AEs and ARs when participants attend for treatment or follow-up
- Using medical judgement in assigning seriousness and causality on events
- Ensuring that all SAEs and SARs, are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.
- Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.

Chief Investigator

- Clinical oversight of the safety of trial participants, including an ongoing review of the risk/benefit.
- Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
- Using medical judgement in assigning expectedness to SARs in line with the RSI.
- Immediate review of all SUSARs.
- Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol.
- Review/assignment of Medical Dictionary for Regulatory Activities (MedDRA) preferred terms System Organ Class coding for all SAEs and SARs.
- Confirming what changes to RSI are required as part of the annual review process of the SmPC.
- Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

Sponsor

- Data collection and verification of AEs, ARs, SAEs, SARs and SUSARs onto a database (may be delegated to NCTU, according to the delegation agreement).
- Reporting safety information to the independent oversight committees for the ongoing assessment of the risk/benefit ratio throughout the life of the trial (may be delegated to NCTU).
- Assessment of expectedness of any SUSARs (delegated to the CI)
- Expedited reporting of SUSARs to the Competent Authority (CA) and REC within required timelines
- Notification of all investigator sites of any SUSAR that occurs (may be delegated to NCTU.
- Reviewing RSI at least annually and notification of PIs of any required updates (may be delegated to NCTU)
- Preparing tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC (may be delegated to NCTU)

TSC/DMC/TOC

- Review of safety data collected to date to identify any trends

9.7 Notification of Deaths

Fatal SUSARs will be reported within 7 days to REC and MHRA. Monitoring of all other deaths will occur via the TMG, IDMEC and the TSC.

All Participant deaths will need to be reported as SAEs, with the reason for death identified on the SAE form and recorded in the eCRF. The only exception to this is death due to progression of CLAD which will be reported in the eCRF, but not as an SAE.

9.8 Pregnancy Reporting

In the event of a study participant or the partner of a study participant becoming pregnant on the trial the site must notify NCTU within 24 hours of becoming aware of the pregnancy and complete a pregnancy reporting form. The pregnancy reporting form should be sent to nctu.ECLAD.conf@nhs.net.

Site must approach the trial participant or the partner of a trial participant to obtain consent to follow to outcome of pregnancy. For the female partner of a male trial participant, an E-CLAD UK Partner Pregnancy Information Sheet will be provided.

In the event that a congenital anomaly or birth defect does occur, this must be reported as a SAE.

9.9 Overdose

Where an occurrence of methoxsalen over-dosing is discovered, this should be notified to the PI immediately and any appropriate care or guidance given to the patient. In the event of methoxsalen overdose, the patient should be kept in a darkened room for at least 24 hours.

An overdose, whether intentional or accidental must also be reported immediately to NCTU (email: e-clad@newcastle.ac.uk). Whilst it is not in itself an adverse event or serious adverse event, any untoward medical occurrence as a result of an overdose, or any condition that leads to an overdose being taken is considered an AE or SAE and should be reported as per section 9.2. Details of the event must be recorded in the case report form for the trial and the participant's medical records.

9.10 Reporting Urgent Safety Measures

An Urgent Safety Measure (USM) is an action that the Sponsor or an Investigator may take in order to protect the subjects of a trial against any immediate hazard to their health or safety. Upon implementation of an USM by an Investigator, the Sponsor, CI and NCTU must be notified immediately and details of the USM given. The Sponsor must inform the MHRA and the NHS REC within 3 days of the USM taking place in accordance with the Sponsor's standard operating procedures. The MHRA may alert the trial team to a new safety signal identified for the trial IMP. In the event of this occurring, the IMP may need to be discontinued with immediate effect and a temporary halt submitted to the competent authorities. The sponsor is required to put the trial on hold with immediate effect.

9.11 Development Safety Update Reports

The following reports will be submitted each year as a condition of the authorisation to undertake a clinical trial or as a condition of a favourable opinion from a REC.

In the UK, a DSUR will be submitted to the MHRA and NHS REC once a year on the date of CTA approval of the trial. NCTU must ensure that the report is submitted within 60 days of the end of the reporting

period. The Trial Management Group must contribute to the compilation of the DSUR with the CI being involved in completion of the relevant sections requiring medical input and assessment of any newly identified risks and the summary of benefit-risk considerations. The CI must review and authorise the final report before it is ready for submission. The DSUR should also be reviewed by the NCTU QA Manager and Sponsor Representative prior to submission. NCTU staff will prepare and submit DSURs for the trial, in accordance with NCTU SOPs.

An NRES CTIMP Safety Report Form will be sent to REC along with the DSUR. Reports of SUSARs in the UK, urgent safety measures and any other safety reports submitted, for example, reports of a data monitoring committee, will also be accompanied by a Safety Report Form.

A NRES Annual Progress Report for CTIMPs will be prepared and submitted by the CI to REC, and copied to Sponsor, on the anniversary date of the REC favourable opinion.

10. STATISTICAL CONSIDERATIONS

The statistical analyses are described in full detail in a separate Statistical Analysis Plan. Statistical analysis will take place after data lock.

10.1 Sample Size Calculation

Our proposed sample size is 90 patients. We used published evidence to underpin our sample size calculations. Todd et al reported changes in longitudinal lung function in 213 CLAD patients who did not receive ECP; 27% had a <10% loss in FEV1 within 6 months, equating to stabilisation. We assume conservatively that in the SOC arm, 30% patients will be responders. The three largest ECP in CLAD studies show 54-61% patients had <10% decline in FEV1 within 6 months; we therefore assume a 55% stabilisation rate in the ECP arm. With 90 patients randomised 1:1 between SOC and ECP arms, we would have 80% power (5% one-sided type I error rate) to detect a difference when the ECP arm has a 55% response rate and the SOC arm a 30% response rate. This calculation assumes Barnard's exact test is used in the analysis.

As the primary endpoint is a composite responder endpoint, our primary analysis will utilise the augmented binary method to test the difference in response rate as the primary analysis (see Section 1010.2). Previous work has shown that the augmented binary method increases the power of the analysis equivalent to increasing the sample size by at least 35% without any inflation in the type 1 error-rate. Even allowing for 10% of patients dropping out, we are thus confident power will be above 85% for this analysis, and believe it is likely to be above 90%. Conservatively, for the augmented binary analysis we believe the maximum number of patients required to achieve 80% power is 68.

10.2 Analysis Populations

All primary analyses of the primary and secondary outcome efficacy analyses will be carried out on an intention to treat basis in the full analysis population. The full analysis population will contain all patients recruited into the study (regardless of whether they were later found to be ineligible, allocated to the incorrect treatment, in violation of the protocol, etc.)

Safety analyses will be carried out similarly, in a safety population consisting of all patients recruited into the study.

Secondary efficacy analyses will be carried out in a per-protocol analysis population. The per-protocol analysis population will consist of the patients who completed a full-course of the treatment they were originally assigned (i.e. 12 weeks of treatment for the ECP plus SOC arm), as per the protocol.

10.3 Statistical Analyses

10.3.1 Analysis of the Primary Outcome Measure

The primary and secondary analyses of the primary outcome will be conducted using the augmented binary method (22). This will utilise a joint model of the change in FEV1 and FVC from baseline to 12 and 24 weeks, leveraging this to estimate the difference in probability of being a responder (no 'rapid decline' at 12 weeks and ≤10% loss in FEV1 and FVC at 24 weeks) between the treatment arms. In addition to an estimated difference, the method will provide a confidence interval for the difference and a p-value for significance testing. The method allows covariates to be adjusted for: we will include the variables included in the stratified randomisation routine as covariates (CLAD phenotype and site).

Sensitivity analyses of the primary outcome will be conducted using a logistic regression model for the binary responder primary outcome, adjusting for CLAD phenotype and site. A second sensitivity analysis will include all participants who had >20% reduction from baseline in FEV1FEV1/FVC at 12 weeks as non-stabilised.

10.3.2 Analysis of Secondary Outcome Measures

Secondary outcomes will be analysed using suitable regression models (e.g. linear regression for continuous outcomes and ordinal regression for ordinal data).

10.3.3 Mechanistic analysis

We will conduct a range of analyses that will explore the mechanism of ECP.

1. To investigate which cell and molecular variables in blood (at baseline) are associated with response, we will fit regression models with responder/non-responder as an outcome and each potential biomarker included (in a separate model) as a baseline covariate.
2. To investigate the trajectories of the cell and molecular variables and how they differ in responders and non-responders, we will fit a longitudinal model for each variable with responder/non-responder as a covariate. This will be done in all patients and then separately in SOC and SOC+ECP patients.
3. To investigate the differential composition of circulating leukocytes, we will model the percentage of blood made up of each cell type and how these change from baseline over time in responders and non-responders using a longitudinal model as described above.
4. To investigate if differences in the transcriptional signature of leukocytes at baseline or changes over time are predictive of response, we will perform both single gene and effector pathway analysis in responders and non-responders across both study arms.
5. To investigate if there is a predictive signature associated with the treatment effect of ECP+SOC vs SOC, we will apply a method developed in Newcastle that extends the adaptive signature design (323). This may detect a 'sensitive' subgroup of patients who strongly benefit from ECP.

These analyses will be exploratory and will help inform a subsequent effectiveness study. The power of the mediation analyses depends on the proportion of responders and non-responders. Assuming

50% of patients are responders, we will have 90% power to detect standardised effect sizes of 0.7. For the Newcastle site, we anticipate a sample size of around 16, which would provide 90% power to detect standardised differences of 1.6. A multiple testing correction will be applied to ensure that the false discovery rate is controlled at 5%.

10.3.4 Subgroup Analyses

We will conduct subgroup analyses (carried out in a similar manner to that of the primary analyses, as described above) to explore the consistency in the efficacy of ECP between the three CLAD phenotypic subgroups. We note that this is exploratory, and the trial sample size has not been chosen to ensure this analysis is well-powered. Subgroup analyses will only take place where it is judged that the available sample size is sufficient for the proposed analysis.

10.3.5 Missing data

We will assess the impact of missing primary outcome data by examining its extent, and whether it is missing at random or is informative. We will consider the use of multiple imputation methods and sensitivity analyses if data is considered missing to a sufficient extent (e.g. approximately >10%). Similar consideration may be made for secondary outcome measures.

10.3.6 Interim Analyses and Criteria for the Premature Termination of the Trial

There is no formal interim analysis. An IDMC of all independent members will be convened to undertake independent review.

11. DATA HANDLING

11.1 Data Collection Tools and Source Document Identification

All data for an individual patient will be collected by each PI or their delegated nominees and recorded in the electronic case report form (eCRF) for the study. The study-specific eCRF will be set up using Redpill, Sealed Envelope's eCRF system. Participant identification on the eCRF will be through a unique trial identifier. Participants cannot be identified from eCRFs or paper data collection tools. The participant's name will be linked to their unique trial identifier via a record filed within each site's ISF, which will be stored in a locked room at site.

A Source Data Agreement will be completed prior to each site opening to screening and recruitment activity; this will document agreed sources of data.

11.2 Data Handling and Record Keeping

The CI has overarching responsibility for collection, quality and retention of data. Data will be collected by an appropriately qualified and delegated member of site personnel. Data will be handled, computerised and stored in accordance with the UK Data Protection Act 2018 and the UK GDPR as amended on 01 January 2021 by regulations under the European Union (Withdrawal) Act 2018, to reflect the UK's status outside the EU, the latest GCP Directive (2005/28/EC) and local site policy. Paper copies of trial-related documentation will be annotated, signed, dated and filed in the Investigator Site

File. Copies of the Summary PIS, PIS, completed written consent form, eligibility forms and letter to GP will be filed in the participant's medical notes.

The CI or designated nominees will continuously monitor completeness and quality of data collected on the trial database. Monitoring will include regular correspondence with site staff to ensure missing data is collected wherever possible and ensuring continuous high quality of data capture. Data completeness and progress reports will be generated for regular review at TMG meetings.

11.3 Access to Data

The site PI and staff formally delegated to do so will have access to source data and the ISF to conduct the trial.

Access to the trial database will be password-limited, with task-specific restrictions (e.g. data entry/randomisation). The site PI will formally delegate database tasks to site staff, by way of dated signatures on the Site Delegation Log.

NCTU trial management staff, representatives of the host institution, Sponsor and the MHRA will be granted access to the source data, ISF and trial database for the purposes of monitoring, audit and inspection respectively. Consent will be sought from the participant for access to their medical records and trial data for the purposes of monitoring, audit and inspection.

Data may be securely downloaded from the trial database and released to the Trial Statistician for analysis, including, as needed, for reports to the IDMEC. Data release will only take place after documented agreement from key members of the TMG.

Site staff, including the PI may not disclose or use for any purpose other than conduct of the trial any data, record or other unpublished confidential information disclosed to those individuals for the purpose of the trial. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said information to other parties.

11.4 Archiving

Trial documents and data will be archived in accordance with UK GCP legislation and as specified in Sponsor and NCTU SOPs. All trial documentation and data will be archived for 5 years.

12. MONITORING, AUDIT & INSPECTION

12.1. Trial Management Group (TMG)

The TMG will be responsible for the day-to-day running of the trial and will consist of the CI, members of NCTU, statistician(s), Sponsor and, as required, other members of the co-applicant team. The TMG will monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. TMG meetings will occur approximately 4-6 weekly. Progress will be monitored proactively according to agreed trial timelines and any issues addressed. The TMG will liaise with the Trial Steering Committee (TSC), providing updates on trial progress and highlighting any issues arising.

12.2. Trial Steering Committee (TSC)

The TSC will be established to provide overall independent oversight of the trial and will oversee trial conduct and progress. The TSC will consist of an independent chair, together with at least two other independent members, a Patient and Public Involvement (PPI) representative and the Chief Investigator. The TSC will meet approximately 6-monthly throughout the trial and meetings may be attended by non-voting observers including those from the NCTU, co-applicant team, Sponsor and Funder.

12.3. Independent Data Monitoring and Ethics Committee (IDMEC)

The IDMEC (also referred to as DMC and IDMC) will consist of at least three independent members including an Independent Chair, an Independent Statistician and an Independent Clinician. The IDMEC will make recommendations to the TSC as to whether there are any ethical or safety issues that may necessitate changes to the trial. The IDMEC will meet approximately 6-monthly throughout the trial.

12.4. Principal Investigator

Each site will be led by a Principal Investigator who will be responsible for trial conduct. They will be supported by research nurses and all site staff will be GCP trained.

The Principal Investigator will be responsible for the oversight of day-to-day trial conduct at site. The NCTU will provide day-to-day support for the site and training, site initiation activities and routine monitoring activities.

12.5. Monitoring

Quality control will be maintained through adherence to Sponsor and NCTU SOPs, trial protocol, GCP principles, research governance and clinical trial regulations.

Monitoring to ensure appropriate trial conduct and data collection will be carried out by NCTU. Electronic data will be stored in secure, password-protected computers. NCTU staff will use a combination of central monitoring, off-site monitoring and on-site monitoring visits to ensure the trial is conducted in accordance with GCP and the trial protocol.

All monitoring findings will be reported and followed up with the appropriate persons in a timely manner. The site PIs and institutions will permit trial-related monitoring, audits, and regulatory inspections, providing direct access to source data and documents relating to the trial. All data will be retained for 5 years.

The CI or designated nominees will continuously monitor completeness and quality of data collected on the trial database. Monitoring will include regular correspondence with site staff to ensure missing data is collected wherever possible and ensuring continuous high quality of data capture. Data completeness and progress reports will be generated for regular review at TMG meetings.

A Site Delegation Log will detail the responsibilities of each member of site staff working on the trial.

Monitoring will be risk-based as detailed in the trial specific monitoring plan. The monitoring plan will be reviewed and amended during the course of the trial based on changes to the protocol and identified or perceived risks.

The trial may be subject to audit by representatives of the Sponsor or inspection by [MHRA/EMA/HTA]. Each investigator site will permit trial-related monitoring, audits and regulatory inspection including access to all essential and source data relating to the trial.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee Review and Reports

The NCTU will obtain a favourable ethical opinion from an NHS REC prior to the start of the trial. All parties will conduct the trial in accordance with this ethical opinion.

The NCTU will notify the REC of all required substantial amendments to the trial and those non-substantial amendments that result in a change to trial documentation (e.g. protocol or patient information sheet). Substantial amendments that require a REC favourable opinion will not be implemented until this REC favourable opinion is obtained. The NCTU will notify the REC of any serious breaches of GCP or the protocol, urgent safety measures or SUSARs that occur during the trial.

An annual progress report will be submitted each year to the REC by NCTU until the end of the trial. This report will be submitted within 30 days of the anniversary date on which the original favourable ethical opinion was granted.

The NCTU will notify the REC of the early termination or end of trial in accordance with the required timelines.

13.2 Peer Review

The protocol has been reviewed and authorised by the Sponsor, CI, NCTU, and the Trial Senior Statistician.

13.3 Public and Patient Involvement

Public and patient participants have been involved throughout the development of this trial; from deciding the research question to discussing the rationale, design, and delivery of the study.

A range of public and patient involvement (PPI) input has informed the development of this trial. The original idea was discussed in Sept 2019 with the NIHR Blood and Transplant Research Unit in Organ Donation and Transplantation (BTRU ODT) Public and Patient Research Panel comprising transplant recipients, family and public members. The panel felt that as CLAD affects 50% of lung transplant recipients, impacting survival, this trial could produce benefits to patient quality and length of life.

The panel emphasised the value of appreciating the lung transplant patient journey; the emotional aspects of waiting for transplant, regaining quality of life post-transplant and the devastation of then developing CLAD which curtails life expectancy. The panel strongly recommended inclusion of qualitative interviews, to enable in-depth exploration of patient experiences of CLAD, its treatment and of ECP.

In Oct 2019, we consulted with the NIHR RDS North East North Cumbria (NENC) Consumer Panel and a national forum of transplant recipients coordinated by the NHS Blood and Transplant Patient and Public Advisory Group. Their input changed our description of ECP and study endpoints in our lay summary. Both groups recognised the need for better treatment of CLAD and gave strong support for the study rationale and potential benefit for participants. These discussions facilitated two lay co-

investigators joining the research team Our lay co-investigators have embedded patient and public perspectives throughout the development of the trial.

In May 2020, we sought PPI on acceptability of the ECP treatment regimen and impact on recruitment. The panel and lay co-investigators felt it inappropriate to ask unselected lung transplant recipients in case of raising concerns among healthy recipients about future CLAD development, especially if discussing a treatment that is not yet openly available. We interviewed four patients receiving ECP who demonstrated a strong sense of treatment acceptability: “never felt like a chore” “don’t find it that bothersome” “it’s quite easy”. This included patients using a tunnelled central venous catheter for their ECP treatment and provided reassurance the regimen would not be seen as overly burdensome.

The panel and lay co-investigators recommended budget provision for a carer to accompany study participants for ECP therapy sessions to provide close support. Very strong support was confirmed for the qualitative study to understand the patient journey. The panel identified themes to explore including social, cultural, economic, physical, and emotional aspects which will support the primary study aims and provide lessons for future implementation.

Ongoing PPI in the trial will be provided by a Public and Patient Advisory Group that will meet regularly to support the trial team by providing input to all participant-facing trial documentation, review progress and assist with dissemination of results.

13.4 Regulatory Compliance

The trial will be conducted in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments. All parties must abide by these regulations and the ICH GCP guidelines.

The NCTU staff will obtain a Clinical Trial Authorisation from the MHRA prior to the start of the trial and will notify the MHRA of any substantial amendments that require review by the competent authority. These substantial amendments will not be implemented until the MHRA and HRA have issued an acceptance of the amendment.

The Sponsor will notify the MHRA of any serious breaches of GCP or the protocol, urgent safety measures or SUSARs that occur during the trial.

The Development Safety Update Report will be submitted each year to the MHRA and REC by NCTU until the end of the trial.

NCTU staff will notify the MHRA of the early termination or end of trial in accordance with the required timelines.

13.5 Protocol Compliance

It is the responsibility of the CI to ensure that the trial is run in accordance with GCP and the protocol. Trial tasks may be delegated to a suitably qualified or experienced member of the trial team, but the CI and PI will retain overall responsibility for adherence to protocol and GCP. The trial will be monitored by NCTU staff, to measure protocol compliance and manage deviations.

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials. The CI will not implement any deviation from the protocol without agreement from the Sponsor, except where necessary to eliminate an immediate hazard to trial participants.

In the event of a deviation from the protocol, the nature of and reasons for the deviation will be recorded on a deviation tracking log and signed off by the PI and NCTU will notify the Sponsor. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC, MHRA and local NHS R&D for review and approvals as appropriate. It is Sponsor policy that waivers to the protocol will not be approved.

For the purpose of avoiding uncertainty, the occurrence of a protocol deviation, violation or serious breach will not lead to withdrawal of the participant from the trial. Once randomised, participants will remain in the trial unless meeting the criteria for withdrawal given in section 5.8.

For sites where the ECP unit falls within a different trust to the research team, if any deviations should occur while the participant is with ECP team/during delivery of ECP treatment, the ECP team must ensure these details are emailed to the research team in a timely manner.

The research team will then include this deviation on the site deviation log and send the updated log to the central trial management team as per usual process.

13.6 Notification of Serious Breaches to GCP and/or the Protocol

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial

The sponsor must be notified immediately of any incident that may be classified as a serious breach. Sponsor will notify the MHRA and the NHS REC within the required timelines in accordance with the Sponsor and NCTU SOP.

13.7 Data Protection and Patient Confidentiality

All investigators and trial site staff will comply with the UK Data Protection Act 2018 and the UK GDPR as amended on 01 January 2021 by regulations under the European Union (Withdrawal) Act 2018, to reflect the UK's status outside the EU, with regards to the collection, storage, processing and disclosure of personal information and will uphold the core principles of the legislation.

Trial data held on computers will be accessible only by authorised study personnel and will be password protected. Paper records containing personal information will only be accessible by trial personnel at each site, central trial personnel, monitors from NCTU and auditors/inspectors from the Sponsor or regulatory authorities.

All data relating to the qualitative sub-study will be sorted securely on password protected computers, on Newcastle University servers and accessible only to authorised sub-study personnel. Transcripts from individual interviews will be anonymised, and no individual will be identifiable in any form of dissemination from the qualitative sub-study.

13.8 Indemnity

NHS indemnity for clinical trials conducted with NHS permission will apply for clinical negligence that harms individuals towards whom the NHS has a duty of care. Indemnity in respect of protocol authorship will be provided through a combination of NHS schemes (for those protocol authors who have substantive NHS employment contracts) and through Newcastle University's public liability insurance (for those who have their substantive contracts of employment with the University).

There is no provision for indemnity in respect of non-negligent harm. NHS Organisations must ensure that site staff without substantive NHS contracts hold honorary contracts to ensure they can access patients and are covered under the NHS indemnity arrangements.

13.9 Amendments

It is the responsibility of the Research Sponsor to determine if an amendment is substantial or not and study procedures must not be changed without the mutual agreement of the CI, Sponsor and the Trial Management Group.

Substantial amendments will be submitted to the REC and/or MHRA (as appropriate) and will not be implemented until this approval is in place. It is the responsibility of NCTU to submit substantial amendments.

Non-substantial amendments will be submitted to the Health Research Authority (HRA) and will not be implemented until authorisation is received.

Substantial amendments and those minor amendments which may impact sites will be submitted to the relevant NHS R&D Departments for notification to determine if the amendment affects the NHS permission for that site. Amendment documentation will provide to sites by NCTU.

13.10 Post-Trial Care

No provision for continuation of trial medication will be made by the trial team or Sponsor. Participants will continue to be cared for by their usual clinical transplant team after the end of the trial. ECP treatment cannot be provided by the trial after participation in the trial has ended. Access to ECP treatment outside of the trial might be possible but this will be dependent on sites being able to make arrangements for this locally. Not all hospitals are able to offer ECP treatment. Participants will be advised to discuss whether this would be an option for them with their clinical team.

13.11 Access to the Final Trial Dataset

Ownership of the data arising from this trial resides with the Sponsor. On completion of the trial, the trial data will be analysed and tabulated, and a final report will be prepared.

14. DISSEMINATION POLICY

14.1. End of Trial Reporting

A final report of the trial will be provided to the Sponsor and REC within 1 year of the end of the trial.

The full trial dataset will be created and uploaded for publishing through the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database, as per the European Commission's guidelines on posting and publication of result-related information within 12 months.

14.2. Authorship Policy

Ownership of the data arising from this trial resides with the trial team and their respective employers. On completion of the trial, the trial data will be analysed and tabulated, and a clinical study report will be prepared.

Authorship eligibility for each manuscript arising from this trial will be determined by the Trial Management Group. All co-applicants, plus the Senior Trial Manager, Trial Manager, Data Manager and Trial Statisticians, will be eligible for authorship on papers reporting the protocol and main trial results, subject to fulfilling the ICMJE authorship criteria. Authorship for other conference abstracts and scientific papers arising from this work will be decided by the Trial Management Group.

All outputs from this programme of work will acknowledge the Newcastle Clinical Trials Unit, Newcastle University, and The Newcastle upon Tyne Hospitals NHS Foundation Trust as Sponsor.

14.3. Publication

The Trial Management Group will complete a Sponsor publication plan, which will be reviewed at least annually.

The final clinical trial report will be used for publication and presentation at scientific meetings. Trial Investigators have the right to publish orally or in writing the results of the trial.

Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

14.4. Making Results Publicly Available

The trial will be prospectively registered on the ISRCTN trial database prior to enrolment of the first participant.

Trial results will be made publicly available on the ISRCTN trial registry within 12 months of the end of the trial, defined as Last Patient Last Visit date.

14.5. Data sharing

Until publication of the trial results, access to the full dataset will be limited to the Trial Management Group and to authors of the publication. At the end of the trial, the de-identified dataset will be prepared and stored by Newcastle University.

Requests for data sharing with bona fide study teams out with Newcastle University or NuTH will be considered by a Data Access Committee, with representation from the Sponsor and CI, and will be subject to presenting a clear plan of what the data will be used for, how the data will be analysed, how the results will be disseminated, and who the authors will be.

Data transfer will be subject to completion of a Data Sharing Agreement between Newcastle University and the end users.

Data will not be withheld from bona fide researchers requesting access unless the above criteria for sharing are not met.

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16. APPENDICES

16.1 Appendix 1 – Approach to Standard of Care in E-CLAD UK Trial Participants

The information in this appendix details the agreed Approach to Standard of Care in E-CLAD UK Trial Participants

Maintenance Immunosuppression:

- Calcineurin inhibitor
- Corticosteroid
- Cell cycle inhibitor

Anti-microbial prophylaxis (if indicated)

- Pneumocystis pneumonia (PCP) prophylaxis lifelong
- Herpes simplex prophylaxis
- Cytomegalovirus (CMV) prophylaxis
- Fungal infection prophylaxis
- Inhaled antibiotic prophylaxis

General Health

- Blood pressure control
- Lipid profiles control
- Bone protection
- Diabetes control
- Optimised nutrition and weight
- Renal protection strategies
- Exercise rehabilitation
- Cancer surveillance

Treatment of Acute Cellular Rejection (ISHLT A2 or above)

- IV methylprednisolone pulse if early or severe
- Oral prednisolone augmentation

Treatment of Acute antibody mediated rejection

- Plasma exchange +/- IV immunoglobulin
- +/- Cyclophosphamide
- +/- Corticosteroids
- +/- Rituximab

Treatment of Acute Infections

- Anti-microbials as clinically indicated driven by culture and sensitivities
- Antibiotics (oral or intravenous)
- Anti-fungals (oral or intravenous)
- Anti-virals as clinically indicated

Treatment of Gastro-oesophageal Reflux

- Proton pump inhibitor

- Pro-kinetic agents
- Anti-reflux surgery if indicated

Standard care of lung transplant recipients with >10% drop in FEV1 and no clear explanation

- Chest x-ray
- Sputum culture if expectorating
- Bronchoscopy with bronchoalveolar lavage and transbronchial lung biopsy
- CT Chest with inspiratory and expiratory views
- Blood for Donor Specific Antibodies
- Exclude extra-pulmonary causes of lung function decline
- Treat any bronchial stenosis with dilatation +/- stenting
- Treat any new or exacerbated existing respiratory infections
- Treat Acute Cellular Rejection if ISHLT A2 or above
- Treat Acute Antibody Mediated Rejection

Standard care of lung transplant recipients with possible CLAD (Pre-study)

- Trial of azithromycin 250-500mg three times weekly for minimum of 6 weeks
- Do not use Leukotriene Receptor Antagonists
- Do not use inhaled corticosteroids
- Monitor for possible reversible causes emerging.

Standard care of lung transplant recipients with probable or definite CLAD (Within study)

- Monitor for and treat any respiratory infections
- Minimise risk of infections with nebulised antibiotics in colonised patients
- Focus on relief of symptoms
- Supplementary Oxygen as needed
- Bronchodilators as needed
- Psychological Support as needed
- Pulmonary rehab as indicated
- Do not use Leukotriene Receptor Antagonists
- Do not use inhaled corticosteroids
- Do not use Total Lymphoid Irradiation

Standard care of lung transplant recipients with definite CLAD (after completion or withdrawal from study)

- Consider any of the following as potential rescue therapies
    - Total Lymphoid Irradiation
    - Extracorporeal Photopheresis if not received within E-CLAD UK trial
    - Other therapies at the discretion of the physician providing usual care
    - Other investigational agents if applicable

16.2 Appendix 2 – Research Blood Analysis

For information about how the research blood samples will be analysed, see the E-CLAD UK laboratory manual which contains all the required standard operating procedures.

16.3 Appendix 3 – Health Economics Introduction

The National Institute for Health Research (NIHR) has recently funded via its Efficiency and Mechanistic Evaluation (EME) Research Programme a randomised controlled trial investigating the use of Extracorporeal photopheresis in the treatment of Chronic Lung Allograft Dysfunction: the E-CLAD UK.[1] This study will address the question "Does Extracorporeal Photopheresis (ECP) therapy given to lung transplant recipients with chronic lung allograft dysfunction (CLAD) halt disease progression and if so by what mechanism?"

ECP therapy may be effective in this situation but whether it represents a good use of scarce health service resources is unclear. It is for this reason that an economic evaluation component is proposed to be added. This component will run in parallel with the E-CLAD UK trial and will use the same recruitment and data collection processes as the E-CLAD UK trial.

For the economic component of the E-CLAD UK Trial there will be two components:

1) A cost analysis, a cost-consequence analysis and a cost-effectiveness analysis of using extracorporeal photopheresis for the treatment of chronic lung allograft dysfunction (CLAD) compared with its non-use at 24 weeks follow-up.

2) A model-based cost-effectiveness analysis of using CLAD compared with its non-use. This model will extrapolate over the estimated lifetime of patients primarily using the 24 week trial follow-up data from E-CLAD UK.

These two components will run in parallel, with final analysis and reporting occurring at the same time as the final analysis and reporting of safety and efficacy data from E-CLAD UK.

Publication of the cost-consequence and cost-effectiveness results will occur at the same time or will follow publication of the main trial report of safety and efficacy data from E-CLAD UK to avoid any problems of prior disclosure of effectiveness data.

Part 1: Cost analysis, cost-consequence analysis and cost-effectiveness analysis

Definitions

A cost analysis simply presents the costs of the resources used to deliver a given technology such as extracorporeal photopheresis (ECP).

A cost-consequence analysis is a form of economic evaluation where costs and outcomes are presented in a disaggregated fashion and it can be used to highlight the trade-offs involved in a decision to more widely adopt ECP. The approach is recommended when evaluating technologies whose mechanism of action and outcomes are complex, but it can also be of use when considering any health technology.

A cost-effectiveness analysis is a form of economic evaluation where the effects of an intervention are combined with costs to produce an incremental cost-effectiveness ratio. In the analysis we will conduct we will combine the impacts on quality of life, morbidity, harms and survival into a single measure, the quality adjusted life year (QALY). Results are presented as the extra cost incurred for the more costly (but more effective technology) to produce one more QALY. This is more commonly presented as the incremental cost per QALY gained. This form of economic evaluation is the main form of economic evaluation used by health care decision-makers and regulators throughout the world.

Methods

Comparators

These will match the intervention and control groups of the E-CLAD UK. Namely, ECP plus standard of care (SOC) versus SOC alone in the treatment of CLAD.

Target population

Adults, 16 years or over who have received a double (bilateral) lung or heart and bilateral lung transplantation that fulfil the ISHLT diagnostic criteria for Chronic Lung Allograft Dysfunction. All participants will need to meet the inclusion criteria of E-CLAD UK.

Cost perspective

Costs will be measures with the perspective of UK National Health Service (NHS) & Personal Social Services (PSS).

Time Horizon

24 weeks, matching the trial follow-up of E-CLAD UK.

Cost Analysis

A cost analysis will be conducted of ECP compared to no ECP over the 24 weeks of the E-CLAD UK trial. Costs will include the cost of delivering the ECP, and impacts on subsequent care (e.g. consultations and hospital admissions) over the 24 week follow-up period.

The costs of the ECP delivery will involve a planned 9 sessions (18 treatments) over a 24-week period. The cost estimates will be derived for a centre level, which is what will be the cost of a centre adopting ECP. The resources used in delivering ECP compared to no use of EP will be based on a microcosting exercise. The microcosting exercise will involve identifying, measuring and costing the use of staff time recorded by job title involved in all aspects of the delivery of the EP, the use of other hospital resources associated with receiving ECP, and ECP hardware and disposables.

Data on use of secondary health care services over the 24-week follow-up period will be captured on an electronic case report form by a research nurse for each trial participant. These data will be combined with unit cost data taken from routine sources, e.g. NHS reference costs.

For each trial participant a total cost over the 24-week follow-up period will be estimated. From this the difference in mean costs between trial arms with be calculated. We will adjust for the range of factors that have been specified as part of an 'adjusted analysis' in the statistical analysis plan for E-CLAD UK to ensure comparability between outcomes.

Cost-consequence analysis

The cost of ECP and of subsequent care for patients compared with no ECP will be presented alongside the trial outcomes from the E-CLAD UK in the form of a cost-consequence analysis. How costs will be derived is presented above and consequences will be related to the headline results of the safety and efficacy analysis conducted in E-CLAD UK.

Cost-effectiveness analysis

For this analysis, QALYs will be estimated over the trial duration based upon responses to the EQ-5D-5L questionnaire. The EQ-5D-5L is being collected at baseline and 24 weeks in the NIHR E-CLAD UK trial.[1] The responses to the EQ-5D-5L at both time points will be converted into health state utility values and QALYs estimated for each trial participant using the area under the curve approach. There is no currently accepted value set for EQ-5D-5L in the UK although one is in development. If an approved value set is developed before this analysis is conducted then this will be used to derive

EQ-5D-5L utility values at baseline and 24 weeks. If not, the EQ-5D-3L index values at baseline and 24 weeks will be estimated using the cross-walk value set[2], as recommended by NICE.[3]

The difference in mean QALYs between the randomised groups in E-CLAD UK will estimated. In this we will control for the EQ-5D-5L utility values at baseline to adjust for any minor imbalances in health at baseline. We will also control for any other factors that have been specified as part of an 'adjusted analysis' in the statistical analysis plan for E-CLAD UK.

The costs data required will come from the cost analysis described above. Data on costs and QALYs will then be brought together into an incremental analysis where the incremental cost per QALY gained will be calculated. This will follow best practice methods and will incorporate both deterministic and stochastic sensitivity analyses. The former will assess the impact of changing key assumptions, e.g. how any missing data are handled. The latter will explore the statistical imprecision surrounding estimates of the incremental cost per QALY gained.

Part 2: Modelled lifetime cost-effectiveness analysis

Rationale

The impacts of using ECP may extend beyond the duration of E-CLAD UK. Failure to consider these longer-term impacts may lead to biased conclusions being drawn. For example, if a treatment increases survival but is initially more costly then, with a short-trial follow-up, this means that any gain in survival over the short follow-up period may be insufficient to offset the higher costs. To overcome this common problem, mathematical modelling approaches are adopted to extrapolate beyond the 24-weeks trial follow-up.

Method

A cost-effectiveness analysis of ECP compared with non-use of ECP will be conducted accounting for any increased life expectancy associated with a reduction in the decline of lung function. The results of this analysis will be presented as the incremental cost per QALY gained over the estimated patient lifetime. The finalised version of the model will make use of data from E-CLAD UK.

The primary outcome measure of the E-CLAD UK is response, which is defined as both stabilisation and no rapid decline over the initial 12 weeks. Stabilisation of lung function occurs if both Forced Expiratory Volume (FEV1) and Forced Vital Capacity (FVC) decline by ≤10% (or improve) over the 24 weeks of treatment. Rapid decline is defined as FEV1 or FVC declining by >20% over the initial 12 weeks. The economic model will extrapolate from these two response outcomes to estimate the impact on survival, quality of life and long-term costs.

A focussed search of literature will be conducted to identify studies investigating survival for different levels of decline in lung function. For example, Kneidinger *et al*.[4] report a hazard ratio for a ≤10% decline to total lung capacity (TLC) compared to >10% decline in TLC, and Mason *et al*.[5] report survival data for FEV1 levels post-transplant. Survival evidence will be used to model survival within a Markov model.

To model quality of life beyond 24 weeks, we will search for evidence of decline in lung function over time and consult clinical experts on how this relates to changes in quality of life. For example, Mason *et al*.[6] and Sithamparanathan *et al*.[7] report decline in FEV1 over time. We will also reanalyse data from the E-CLAD UK trial to explore the relationship between the change in rate of decline in FEV1 (a secondary outcome in the E-CLAD UK Trial) with changes in EQ-5D-5L utility values also estimated as part of the E-CLAD UK trial will also provide evidence for the decline in FEV1 for patients receiving ECP and receiving standard of care.

Cost data will come from the Cost analysis described above but we will also reanalyse data from the E-CLAD UK trial to explore the relationship between the rate of decline in FEV1 with total cost at the end of the trial follow-up period. In addition, clinical experts will be consulted on healthcare resource use incurred beyond 24 weeks. These data will be used to assign costs to each element of the Markov model.

Once probabilities, utilities and costs (the model parameters) have been assigned to the Markov model the model will be rolled back to estimate average total costs, life years and QALYs for both EP compared to the non-use of ECP. From these the incremental cost per QALY gained over a life-time long time horizon will be estimated.

Following best practice recommendations we will assign each model parameter a statistical distribution to reflect the imprecision in estimates. In a probabilistic sensitivity analysis we will use Monte Carlo Simulation methods to estimate credible intervals surrounding the difference in QALY and the difference in costs. We will also present the imprecision surrounding estimates of cost-effectiveness.

In addition to the probabilistic sensitivity analysis we will also conduct deterministic sensitivity analysis. Key aspects of this will be to explore assumptions made around extrapolating the effectiveness of ECP. Specifically, we will explore different assumptions about the outcomes following the cessation of ECP treatment at 24 weeks. We will also explore using threshold analysis what gain in QALYs would be needed for ECP to be cost-effective to warrant giving ECP to responders at 24 weeks a further 24 weeks of therapy.

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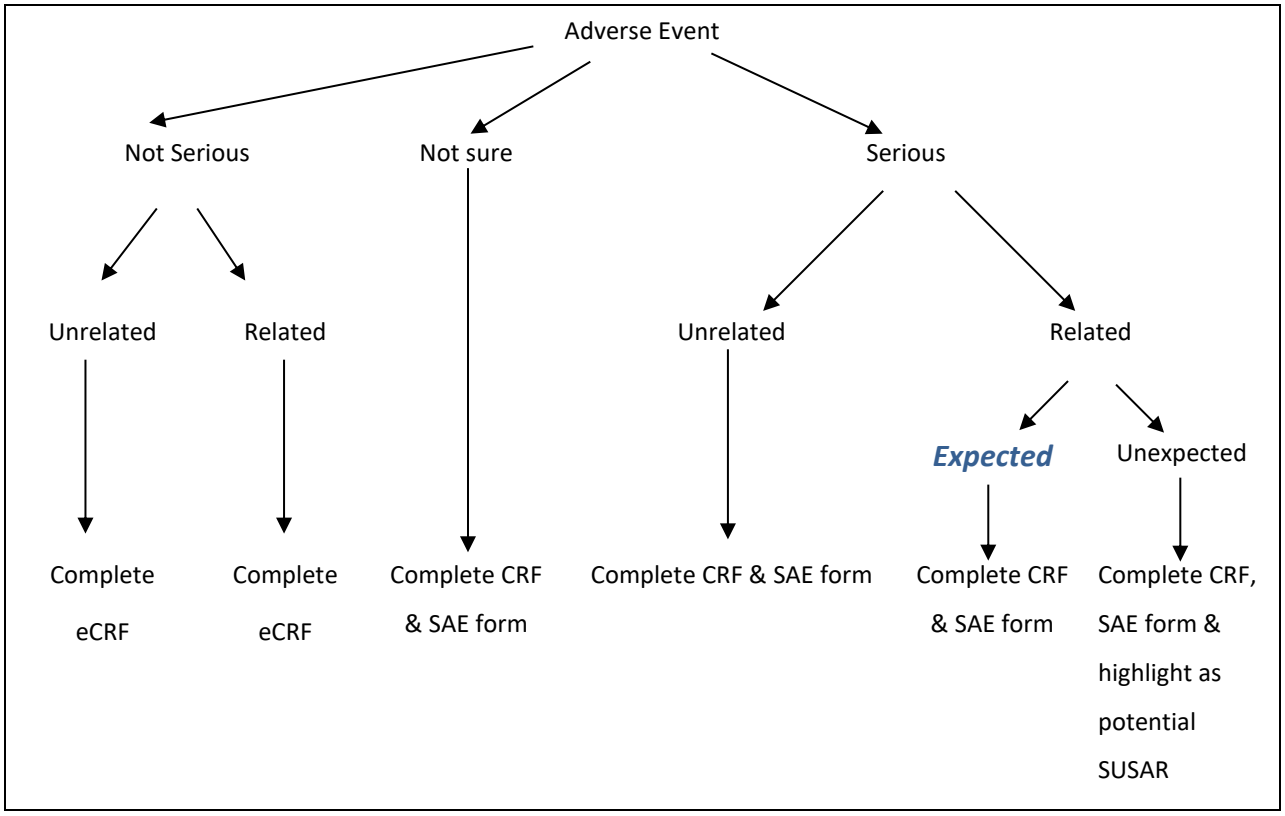
16.4 Appendix 4 - Safety Reporting Diagram

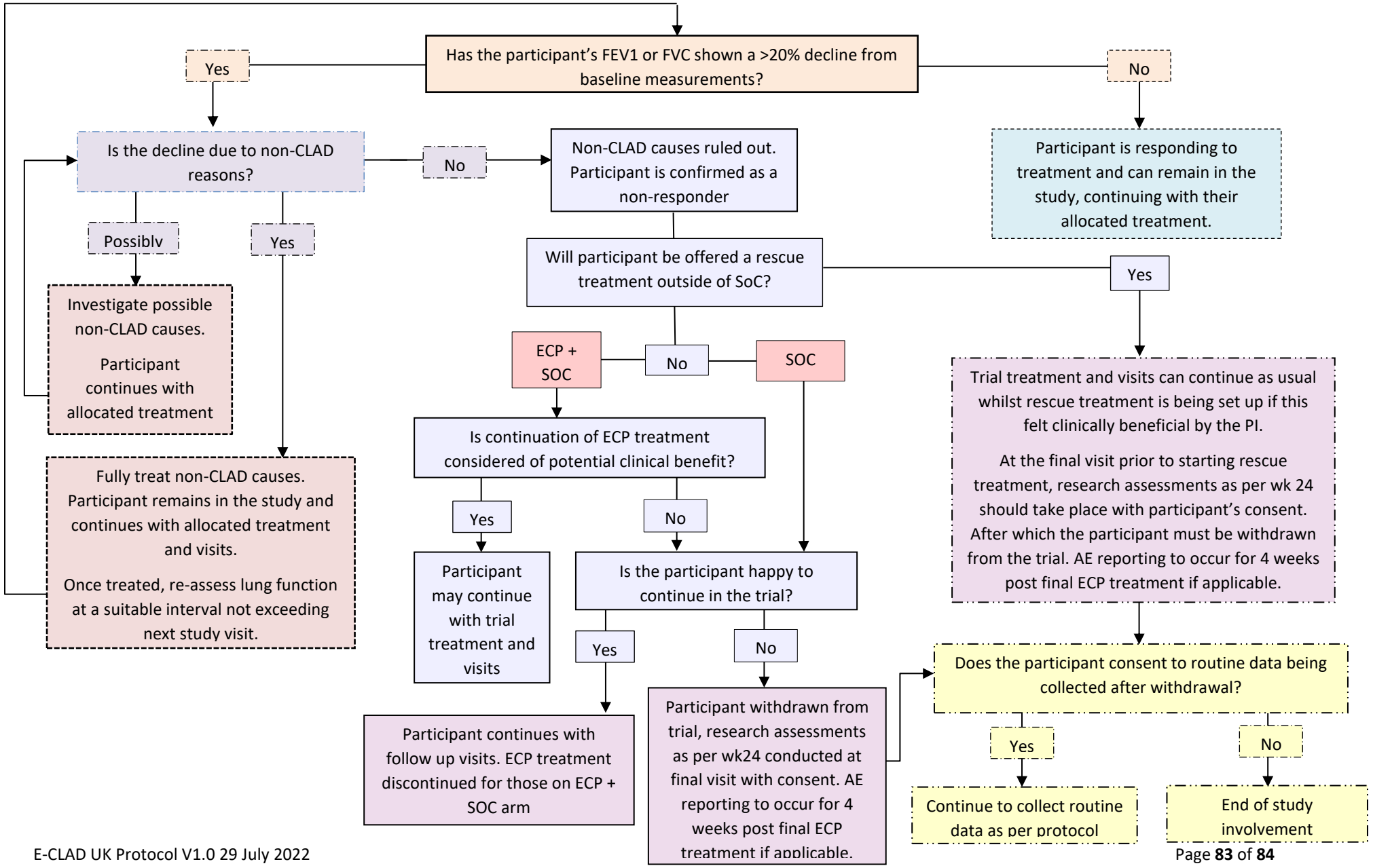


Contact details for reporting SAEs and SUSARs

Please send SAEs form(s) via nctu.E-CLAD.sae@nhs.net

Please ensure that no participant identifiable information is included within the SAE form

16.5 Appendix 5 – Non Responder Decision Tree



16.6 Appendix 6 - Amendment History

Amendment Number	Protocol version no.	Date issued	Author(s) of changes	Details of changes made