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Extracorporeal photopheresis (ECP) in the treatment of chronic lung allograft dysfunction (CLAD): a prospective, multicentre, open-label, randomised controlled trial studying the addition of ECP to standard care in the treatment of bilateral lung transplant patients with CLAD (E-CLAD UK)

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ABSTRACT

Background Long-term survival after lung transplantation is limited compared with other organ transplants. The main cause is development of progressive immune-mediated damage to the lung allograft. This damage, which can develop via multiple immune pathways, is captured under the umbrella term chronic lung allograft dysfunction (CLAD). Despite the availability of powerful immunosuppressive drugs, there are presently no treatments proven to reverse or reliably halt the loss of lung function caused by CLAD. The aim of the E-CLAD UK trial is to determine whether the addition of immunomodulatory therapy, in the form of extracorporeal photopheresis (ECP), to standard care is more efficacious at stabilising lung function in CLAD compared with standard care alone.

Methods and analysis E-CLAD UK is a Phase II clinical trial of an investigational medicinal product (Methoxsalen) delivered to a buffy coat prepared via an enclosed ECP circuit. Target recruitment is 90 bilateral lung transplant patients identified as having CLAD and being treated at one of the five UK adult lung transplant centres. Participants will be randomised 1:1 to intervention plus standard of care, or standard of care alone. Intervention will comprise nine ECP cycles spread over 20 weeks, each course involving two treatments of ECP on consecutive days. All participants will be followed up for a period of 24 weeks.

The primary outcome is lung function stabilisation derived from change in forced expiratory volume in one second and forced vital capacity at 12 and 24 weeks compared with baseline at study entry. Other parameters include

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Chronic lung allograft dysfunction (CLAD) is the main contributor to the limited average life expectancy seen after lung transplantation.
⇒ At present there are no proven treatments for reversing or reliably halting the damage to the transplanted lungs caused by CLAD.
⇒ There is retrospective, single-centre, uncontrolled data to suggest that the addition of extracorporeal photopheresis (ECP) to standard care is beneficial in stabilising lung function in selected patients with CLAD.

WHAT THIS STUDY ADDS

⇒ High-quality, randomised control trial data on the efficacy and safety of the addition of ECP in the treatment of CLAD in bilateral lung transplant recipients.
⇒ An understanding of the mechanisms of action of ECP treatment in CLAD and potential identification of predictive biomarkers of response to treatment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study will provide high-quality data to inform the decisions of clinicians, patients and healthcare commissioners on whether ECP should be included as part of standard care for the treatment of CLAD.
⇒ Predictive biomarkers may allow a personalised decision on which patients with CLAD should receive ECP treatment.

change in exercise capacity, health-related quality of life and safety. A mechanistic study will seek to identify molecular or cellular markers linked to treatment response and qualitative interviews will explore patient experiences of CLAD and the ECP treatment.
A patient and public advisory group is integral to the trial from design to implementation, developing material to support the consent process and interview materials.
Ethics and dissemination The East Midlands—Derby Research Ethics Committee has provided ethical approval (REC 22/EM/0218). Dissemination will be via publications, patient-friendly summaries and presentation at scientific meetings.
Trial registration number EudraCT number 2022-002659-20; ISRCTN 10615985.

INTRODUCTION

For patients with life-threatening chronic lung disease, lung transplantation is the only treatment offering a meaningful improvement in survival and quality of life. In 2021, almost 6500 lung transplants were performed around the world.[1] However, long-term survival after lung transplantation is significantly poorer than that for other organ transplants, with median survival after transplantation being just 6 years.[2] This is predominantly due to the development of progressive immune-mediated damage to the lung allograft resulting in chronic inflammation and fibrosis either around the airways, known as bronchiolitis obliterans syndrome (BOS); or within the lung parenchyma, known as restrictive allograft syndrome (RAS). These phenotypes can occur separately or coexist in a mixed phenotype[3] and are grouped under the umbrella term chronic lung allograft dysfunction (CLAD).[4] In 2019, the requirements for a CLAD diagnosis were changed to remove patients who responded to long-term macrolide antibiotic use. CLAD is now only diagnosed if lung function continues to decline despite an appropriate duration trial of azithromycin therapy.[4 5]

At present, the immune mechanisms driving CLAD are not well understood, with no treatments proven to reverse or reliably halt the damage and loss of lung function.[6] The current standard of care (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, antifibrotic and anti-inflammatory drugs, mesenchymal stem-cells and extracorporeal photopheresis (ECP).[7] For those who develop severe CLAD, retransplantation is currently the only hope. However, many are not suitable due to the presence of comorbidities such as renal dysfunction, frailty and colonisation with resistant organisms.[8] This highlights the urgent need to identify new treatments that can arrest the alloimmune mechanisms driving CLAD, preserving longevity and quality of life, while also removing the need for possible retransplantation.

Immunomodulation by ECP

ECP, an immunomodulatory therapy widely approved for use in conditions such as graft versus host disease after haematopoietic stem cell transplantation and cutaneous T-cell lymphoma, may offer hope in lung transplantation.[9] A generally safe and well-tolerated therapy, ECP involves connecting a patient via an intravenous line to a leukapheresis machine that separates leucocytes from whole blood in a buffy coat. The red blood cells are immediately returned to the patient while the leucocytes are treated with methoxsalen, a photosensitising agent, before being exposed to ultraviolet A (UVA) light to induce apoptosis. The preapoptotic leucocytes are then returned to the patient's circulation where they exert immunomodulatory effects. ECP can be performed in an entirely automated enclosed circuit at the patient's bedside. The treatment can be delivered in either an outpatient or inpatient setting.

ECP has shown promise in slowing or halting the loss of lung function in lung transplant recipients with CLAD.[10] However, these data come from universally single-centre retrospective studies with a lack of proper untreated controls and with ECP delivered only to selected patients with CLAD. The best proof of concept evidence comes from four larger studies that represent a collective population of 223 lung transplant recipients with CLAD, including both RAS and BOS phenotypes.[11–14] This means there is a lack of high-quality randomised controlled trial evidence of the efficacy and safety of ECP in CLAD treatment.

TRIAL OBJECTIVES

E-CLAD UK is a prospective, 2-arm, randomised, open-label clinical trial. The primary objective is to establish whether the addition of immunomodulation via ECP to standard care is more efficacious at stabilising lung function in lung transplant recipients with CLAD compared with standard care alone. Secondary objectives are to determine how the different treatment strategies affect other outcomes including rate of decline in lung allograft function, exercise capacity, disease severity, health-related quality of life, survival and treatment safety over the 24-week trial period. It is designed to collect evidence on the efficacy and safety of ECP for CLAD necessary to inform decisions by clinicians, patients and healthcare commissioners globally regarding its place in the management of lung transplant recipients.

METHODS AND ANALYSIS

Trial methods and analysis are reported as per Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines[15]

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 (The Newcastle upon Tyne Hospitals NHS Foundation Trust, Manchester University NHS Foundation Trust, University Hospitals Birmingham NHS Foundation Trust, Royal Brompton & Harefield Hospitals and Royal Papworth Hospital NHS Foundation Trust). This will allow all adult UK bilateral lung transplant recipients who develop CLAD to learn about the trial and decide if they wish to participate. Two of the centres (Royal Papworth Hospital NHS Foundation Trust and Manchester University NHS Foundation Trust) do not have their own ECP centre and so will be supported by other organisations (Cambridge University Hospitals NHS Foundation Trust and NHS Blood and Transplant, respectively) to provide the study intervention.

Eligibility

The target population for E-CLAD UK is 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 International Society for Heart and Lung Transplantation (ISHLT) 2019 diagnostic criteria for CLAD. The specific eligibility criteria are detailed in box 1.

Intervention

Standard of Care

The standard management of lung transplant recipients both before and after the development of CLAD may vary between centres. However, the underlying principles are well aligned in terms of the approach to maintenance immunosuppression regimen (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[4] 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.

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. Participants in the trial will not be treated with any immunomodulatory interventions such as total lymphoid irradiation or ECP as part of the SOC arm. This will be the

Box 1 Eligibility criteria for the E-CLAD UK trial

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 International Society for Heart and Lung Transplantation 2019 consensus 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 thorax and bronchoscopy+/-transbronchial biopsy within 12 weeks of first CLAD diagnosis.
⇒ Adequate treatment of potential non-CLAD causes of a decline in lung function (eg, acute cellular or acute humoral rejection, infections, airway anastomotic strictures and medical treatment for gastro-oesophageal reflux).
⇒ Progressive decline in forced expiratory volume in 1 second (FEV1) (≥10%), while on azithromycin for ≥6 weeks.
⇒ Capacity to provide written informed consent.
⇒ A minimum of two recorded FEV1 and forced vital capacity (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.

Exclusion criteria

⇒ Single lung transplant recipients.
⇒ Female patients who are breast feeding, pregnant or planning to become pregnant during the timeframe of study participation.
⇒ Current treatment with or history of Total Lymphoid Irradiation 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 haematopoietic 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.
⇒ Coexisting 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 $>25\times10^9$/L.
⇒ Significant heart disease or severe anaemia causing inability to tolerate blood volume shifts associated with ECP.

Continued

Box 1 Continued

⇒ 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 coexisting 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.

approach in both arms of the study, with use of ECP in the treatment arm the only difference.

Extracorporeal Photopheresis

ECP therapy is performed using the Therakos Cellex Photopheresis System which is an automated enclosed system that separates a given volume of the patient's whole blood into plasma, red blood cell and leucocyte fractions. The red cells and some of the plasma are immediately returned to the patient while the leucocytes and remaining plasma are collected in a separate chamber. This collection process is repeated over a number of cycles. The buffy coat suspension of leucocytes is then treated with the photosensitising drug UVADEX (methoxsalen). After the cells have absorbed this drug, they are exposed to UVA light radiation to activate the apoptosis pathway, and then returned to the patient's circulation.

For this trial, UVADEX solution is an investigational drug. The dose of UVADEX used to inoculate cells will be calculated based on the standard treatment volume formula. Heparin is the standard anticoagulant for use with the Therakos Cellex Photopheresis System, however sites will be able to use other anticoagulants if routinely used as part of their standard local ECP protocol, or if heparin is contraindicated for a patient.

Patients will receive nine cycles of ECP, each cycle consisting of two treatments performed on consecutive days, each taking 2–3 hours to complete. Cycles are performed every 2 weeks for the first 12 weeks and then every 4 weeks for the next 8 weeks meaning that those who complete the study will have received nine cycles of ECP over 20 weeks equating to 18 individual treatments (figure 1).

Outcomes

The primary outcome measure is lung function stabilisation derived from the change in forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) at 12 and 24 weeks compared with baseline at study entry. This is a binary composite responder outcome, defined as both 'lung function stabilisation' from baseline to 24 weeks and 'no early rapid decline' as measured from baseline to 12 weeks (figure 2). Lung function stabilisation is classed as a less than 10% fall in both FEV1 and FVC at 24 weeks compared with baseline. Early rapid decline is defined as a more than 20% fall in either FEV1 or FVC from baseline to 12 weeks due to progressive CLAD.

Secondary outcome measures in the E-CLAD UK trial include other measures of lung function, physical performance, health-related quality of life and physical well-being:

1. rate of decline in lung allograft function measured using spirometry (FEV1 and FVC) at baseline and 24 weeks;
2. exercise capacity measured using distance walked in the 6-minute walk test at baseline and 24 weeks;
3. disease severity measured by CLAD classification as per ISHLT guideline at baseline and 24 weeks;
4. health-related quality of life measured by the SF-36v2 and EQ-5D-5L questionnaires at baseline and 24 weeks;
5. survival collected from medical records at 24 weeks and
6. safety measured by collecting details of adverse events (AEs) and serious adverse events (SAEs) occurring between baseline and 24 weeks.

Mechanistic substudy

A mechanistic evaluation of participants' immune responses will be undertaken to understand how these change before and after commencing ECP therapy and to identify if there are any molecular or cellular markers which may help predict patient response to ECP treatment. Blood samples will be collected to characterise immune responses occurring in recipients responding to ECP compared with non-responders, and those receiving SOC alone, to identify potential mechanisms of action. Data will be analysed to determine if CLAD phenotype, clinical factors or immunological markers in blood can predict who will benefit from ECP. Samples for the mechanistic substudy will only be collected from participants from The Newcastle upon Tyne Hospitals NHS Foundation Trust randomised to receive ECP and who provide separate informed consent.

Qualitative substudy

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

Individual semistructured interviews will be carried out with up to 30 patients with CLAD including 20 who have experienced ECP, purposively sampled from those who consented to be approached about the qualitative substudy. Separate informed consent will be collected for participation in the qualitative substudy. Interviews will provide new insights about patient experiences of CLAD as well as providing valuable information about experiences of receiving ECP therapy which will inform future wider implementation. Data will be analysed following the principals of Constructivist Grounded Theory and will employ the constant comparative method.[16 17] Fully anonymised excerpts of data from interview transcripts will be

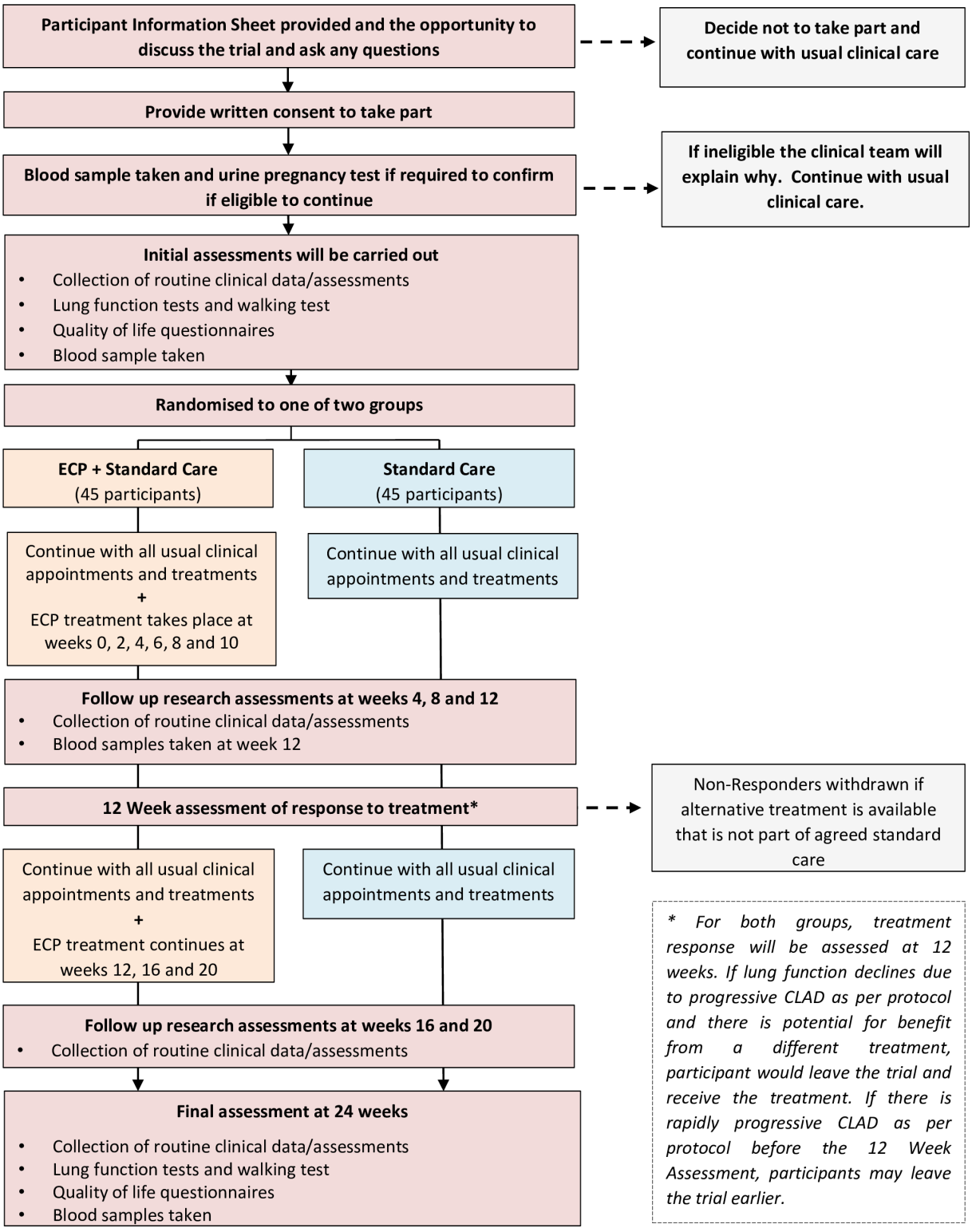

Figure 1 Flowchart of research activity for the E-CLAD UK trial. CLAD, chronic lung allograft dysfunction; ECP, extracorporeal photopheresis.

shared and discussed with our lay applicants and Patient and Public Involvement and Engagement advisory panel.

Participant timeline

All adult lung transplant recipients remain under life-long follow-up at transplant centres and will be familiar to clinical teams. Patients will be identified in clinical practice and potentially eligible patients will be initially approached by the treating clinician. They will be invited to watch a trial information video (https://research.ncl.ac.uk/e-claduk/) and given a short version patient information sheet (PIS) (see online supplemental material).

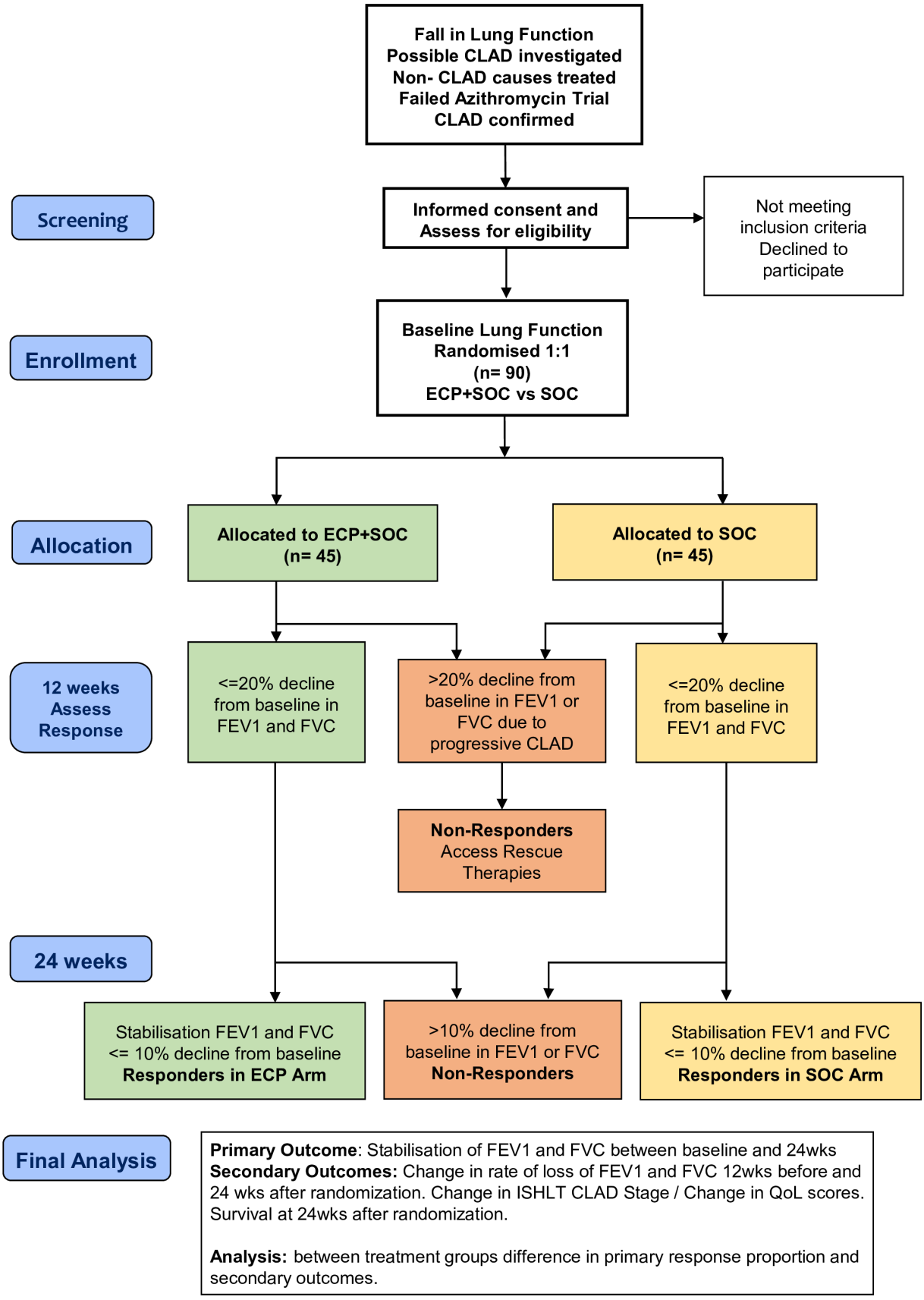

Figure 2 Summary of E-CLAD UK trial primary outcome measure process. CLAD, chronic lung allograft dysfunction; ECP, extracorporeal photopheresis; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; ISHLT, International Society for Heart and Lung Transplantation; SOC, standard of care.

If after watching the video and reading the short PIS they remain interested, patients will be provided with the full PIS to read (see online supplemental material). Willing participants will then be booked in for a baseline visit, at least 24 hours after provision of the full PIS. Eligibility assessments and baseline assessments will take place after consent is given.

For those randomised to ECP, the first ECP cycle will be scheduled within 14 days of the baseline visit. All other visits will be scheduled based on the first ECP treatment date. ECP therapy will take place every 2 weeks for the first 12 weeks and then every 4 weeks until nine cycles are completed by week 20. Research visits will take place for all participants every 4 weeks after the week 0 visit. For participants randomised to the SOC arm, this will be based on the date of consent. These visits will be scheduled to correspond with routine clinical appointments. A final visit will take place for all participants at 24 weeks where final research assessments will occur.

At the week 12 visit, all participants will be assessed for treatment response. Those identified as 'non-responders' due to rapid progression of CLAD will be considered for rescue treatment outside the trial and withdrawn from the trial if necessary. Non-response is defined as a more than 20% drop in FEV1 or FVC compared with baseline at trial entry that is confirmed as being due to progressive CLAD. In the event of trial withdrawal, with consent, week 24 assessments will take place at a participant's final visit.

Allocation

Participants will be randomised 1:1 to receive either ECP plus SOC or SOC alone using a computer-generated randomisation system (Sealed Envelope) with concealed allocation. A balanced allocation will be achieved within the two trial arms by use of two stratification variables, study site and CLAD phenotype, namely BOS, RAS or mixed.

Biological samples

Blood samples will be collected from all participants at study baseline, 12 and 24 weeks for evaluation of immune response. Samples will undergo immunophenotyping, immune marker and transcriptomic analysis. Any samples remaining at the end of the study will be anonymously biobanked for further related analysis outside of the trial.

AEs and assessment process

AEs will be monitored throughout the study from time of consent to end of trial participation through regular face-to-face visits. All participants in the ECP arm will be followed up for a minimum of 4 weeks after their last ECP treatment. Data from all AEs will be recorded on the trial database. SAEs will be assessed for any relationship to the treatment intervention (causality), by a delegated, medically qualified site doctor. Any events believed by the investigator to be due to the progression of CLAD, or any scheduled hospitalisations, including for ECP treatment, will not be reported as SAEs to the Sponsor. The chief investigator will assess, on behalf of Sponsor, expectedness of any serious adverse reactions against the approved reference safety information for the trial.

Data collection and management

All data 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 Red Pill, Sealed Envelope's eCRF system. Participant identification will be through a unique trial identifier.

Access to the trial database will be password-limited, with task-specific restrictions. Only staff formally delegated to do so will have access to the database. Newcastle Clinical Trials Unit (NCTU) staff will monitor trial conduct and data integrity in accordance with the trial monitoring plan.

Statistical methods

Our proposed sample size is 90 patients. Todd *et al* reported changes in longitudinal lung function in 213 patients with CLAD who did not receive ECP; 27% had a <10% loss in FEV1 within 6 months, equating to stabilisation.[18] Therefore, based on best available data, we assume conservatively that in the SOC arm, 30% of patients will be responders. The three largest ECP in CLAD studies[11–13] show that 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, there is 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 and on the basis of a binary primary endpoint. However, as the primary endpoint is a composite responder endpoint, the primary analysis will use the augmented binary method to examine the difference in response rates.[19] It is estimated from previous simulation results that this would increase the power of the trial to >90% without inflation in type I error rate.[20]

Sensitivity analyses of the primary outcome will be conducted using a logistic regression model for the binary responder primary outcome. Secondary outcomes will be analysed using suitable regression models (eg, linear regression for continuous outcomes and ordinal regression for ordinal data). All primary analyses of the primary and secondary outcome measures will be carried out on an intention to treat basis in the full analysis population. This will contain all patients recruited into the study. Safety analyses will be carried out in a population consisting of all patients recruited into the study.

Management and oversight

A Trial Management Group (TMG), consisting of the chief investigator, key NCTU staff, coapplicants, trial statisticians,

local research staff and an NHS Sponsor representative, will meet approximately monthly throughout the duration of the trial. A Trial Steering Committee (TSC), which has an independent chair and four independent members including one patient and public involvement representative, will review study progress and provide advice on all aspects of the trial to the TMG. A Data Monitoring Committee, with an independent chair and two independent members, will monitor data including safety and efficacy as well as the overall conduct of the study, reporting to the TSC. An active risk register has been compiled in consultation with the Sponsor. This will be monitored and updated throughout the trial.

Patient and public involvement (PPI)

Public and patient contributors have been extensively involved throughout the development of the trial; from deciding the research question to discussing the rationale, design and delivery of the study. The original idea for the trial was discussed with the NIHR Blood and Transplant Research Unit in Organ Donation and Transplantation Public and Patient Research Panel who supported the trial, feeling it could improve patients' quality of life and potentially help them to live longer. The panel emphasised the value of understanding the lung transplant patient journey, resulting in the inclusion of qualitative interviews to explore in-depth the patient experiences of CLAD, its treatment and of ECP.

Current ECP recipients have shared their views on treatment acceptability, providing reassurance that the proposed ECP regimen would not be seen as overly burdensome. Lay coinvestigators are part of the research team, helping embed patient and public perspectives throughout the development of the trial, in particular the qualitative work. Long-term PPI in the trial is facilitated through a Public and Patient Advisory Group; members have improved the clarity, inclusivity and accessibility of participant-facing documentation, including patient consent materials and will help review progress and assist with the dissemination of results.

Trial status

The E-CLAD UK trial was opened to recruitment on the 9 February 2023. Recruitment is due to close on 30 June 2025 with the Last Patient Last Visit expected in December 2025. This manuscript is based on Protocol V.2.0 dated 14 October 2022.

Ethics and dissemination

Ethics

A favourable ethical opinion has been granted from the UK Health Research Authority Research Ethics Committee (East Midlands—Derby; REC reference 22/EM/0218). The trial has also received approval from the UK Medicines and Healthcare products Regulatory Agency (MHRA; trial reference CTA 17136/0302/001-0001). The trial has been included in the National Institute for Health and care Research Clinical Research Network (NIHR CRN) portfolio (NIHR CRN study ID: 53956). The trial Sponsor is the Newcastle upon Tyne Hospitals NHS Foundation Trust (tnu-tr.sponsormanagement@nhs.net). The trial Sponsor has delegated responsibility for trial management to NCTU, including trial design; review and approval of all localised patient-facing documentation prior to implementation at each site; collection, analysis and interpretation of data; writing of the protocol publication and final clinical report manuscripts.

Dissemination policy

A final report of the trial will be provided to the Sponsor, funder and Research Ethics Committee within 12 months of the end of the study. The full trial dataset will be uploaded to the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database within 12 months as per the European Commission's guidelines on posting and publication of result-related information. The trial is registered on the ISRCTN trial database and trial results will be made publicly available within 12 months of the end of the trial, defined as Last Patient, Last Visit date.

The final clinical trial report will be used for publication and presentation at scientific meetings. Summaries of results will also be made available to investigators for dissemination within their clinical areas where appropriate and according to their discretion.

DISCUSSION

There is a major unmet clinical need to improve the long-term outcomes for patients undergoing lung transplantation. Despite progress in surgical and the early postoperative management of lung transplant recipients, the development of CLAD remains a major factor contributing to significant morbidity, reduced quality of life and premature mortality. Studies designed to test interventions for the treatment of CLAD have been extremely limited and have historically been single-centre, uncontrolled studies. The E-CLAD UK trial therefore brings an innovative approach to testing a potential treatment for CLAD in addition to current SOC and compared with SOC alone. As a multicentre, randomised controlled trial, the evidence the trial will generate should answer the question as to whether ECP should become a new SOC for lung transplant recipients with CLAD.

The design of E-CLAD UK allows for a formal assessment of a patient's response to their treatment arm at the midpoint of their participation. This allows those with rapidly progressing disease to be identified early as non-responders and offered access to other treatment modalities outside the trial, including access to other clinical trials if eligible. This was felt to be an essential element of the trial design by our public and patient advisory group who felt without this element of the design that recruitment potential would be negatively impacted. This also counteracts concerns by some clinicians levelled at the ethical justification of randomised controlled trials in the treatment of CLAD. However, without

such trials it will be impossible to generate an evidence base that supports personalised treatment for patients with the aim of extending life and maintaining quality of life after lung transplantation.

E-CLAD UK is an unblinded randomised controlled trial and this brings with it an inherent risk of bias. The investigators did consider the viability and appropriateness of conducting a sham ECP treatment in the SOC arm. However, for several significant reasons, including unnecessary participant travel, discomfort and risk from unnecessary venous cannulation, an open-label approach was adopted.

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Contributors AJF conceptualised the study. All authors contributed to either development of the E-CLAD UK funding application or the trial protocol. MW wrote the first draft of the manuscript. AJF, LV, AB, MB, TC, HH, NG, JMSW, HS, MW, CE, LF, JP, JL, AB-N, AK, SR and RE were involved in reviewing and editing the manuscript and have given final approval of the submitted version.

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Competing interests AJF has received honoraria for speaking at educational meetings organised by Mallinckrodt Pharmaceuticals.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by East Midlands - Derby Research Ethics Committee 22/EM/0218 Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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