NIHR HTA Programme

03 October 2012

The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the NIHR

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A Study of Donor Ex-Vivo Lung Perfusion in UK Lung Transplantation

DEVELOP-UK

ISRCTN Number (44922411)

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Sponsored by The Newcastle upon Tyne Hospitals NHS Foundation Trust

DEVELOP-UK

A Study of Donor Ex-vivo Lung Perfusion in United Kingdom Lung Transplantation

Newcastle University

HTA NIHR Health Technology Assessment programme funded project

NHS

In association with

CYSTIC FIBROSIS TRUST

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Emergencies arising outside the study sites should be managed in line with normal clinical care and then discussed in the usual way with the patients' own lung transplant team. In the event that the emergency is felt to be related to the study then contact the appropriate transplant centre where the patient underwent lung transplant and ask to be put through to the appropriate local Principal investigator as listed below:

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Papworth Hospital, Cambridge	01480 830 541 ask for Mr Steven Tsui
Harefield Hospital, London	01895 82 3737 ask for Mr Andre Simon
Wythenshawe Hospital, Manchester	0161 998 7070 ask for Professor Nizar Yonan
Queen Elizabeth Hospital, Birmingham	0121 627 2000 ask for Mr Jorge Mascaro

If further information is required please contact Freeman Hospital on 0191 233 6161 and ask for Professor Andrew Fisher, Chief Investigator to be contacted via mobile phone or contact Mater Hospital, Dublin on 00 353 1830 1122 and ask for Ms Karen Redmond, surgical lead and co-lead investigator to be contacted by mobile phone.

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Study Website
www.develop-uk.net

1. Protocol signature page

1.1 Protocol authorisation signatories

Signature …… Date ……

Professor Andrew Fisher, Chief Investigator

Signature …… Date ……

Dr Tom Chadwick, Statistician

Signature …… Date ……

Dr Jennifer Wilkinson, Senior Trial Manager

1.2 Principal/Chief Investigator signature

I confirm that I have read and understood protocol version 3.0 dated 24 August 2012. I agree to comply with the study protocol, the principles of GCP, research governance, clinical trial regulations and appropriate reporting requirements.

Signature …… Date …….....

Print Name……

Site Name/I.D. ……..

2. Contents Page

3. Glossary of Abbreviations

Abbreviation	Definition
AE	Adverse Event
ANCOVA	Analysis of Covariance
ARDS	Acute Respiratory Distress Syndrome
BAL	Bronchoalveolar Lavage
BP	Blood pressure
CJD	Creutzfeldt-Jakob Disease
vCJD	Variant Creutzfeld-Jakob Disease
CTIMP	Clinical Trial of Investigational Medicinal Product
DBD	Donation after Brain Death
DCD	Donation after Circulatory Death
DLS	Disposable Lung Set
DMEC	Data Monitoring & Ethics Committee
e-CRF	electronic Case Report Form
ELISA	Enzyme-Linked Immunosorbent Assay
ET	Endotrachael Tube
EVLP	Ex-vivo Lung Perfusion
FEV_1	Forced Expiratory Volume in 1 Second
FiO_2	Fraction of Inspired Oxygen
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GP	General Practitioner
GIA	GIA™ brand of cutting stapler from Covidien
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HTA	Health Technology Assessment Programme

IL-6	Interleukin-6
IL-8	Interleukin-8
IL-10	Interleukin-10
ISHLT	International Society for Heart and Lung Transplantation
ITU	Intensive Therapy Unit
MRC	Medical Research Council
NCG	NHS National Commissioning Group
NCTU	Newcastle Clinical Trials Unit
NHSBT	NHS Blood and Transplant
NIHR	National Institute of Health Research
NRES	National Research Ethics Service
ODA	Operating Department Assistant
PA	Pulmonary Artery
PAP	Pulmonary Artery Pressure
PEEP	Positive End Expiratory Pressure
PGD	Primary Graft Dysfunction
PI	Principal Investigator
PO_2	Partial Pressure of Oxygen
PV	Pulmonary Vein
PVR	Pulmonary Vascular Resistance
R&D	Research and Development
QoL	Quality of Life
REC	Research Ethics Committee
SAEs	Serious Adverse Events
SF-36	Short-Form 36 Questionnaire
SF-6D	Short-Form 6D Questionnaire
SNOD	Specialist Nurses for Organ Donation

SOPs	Standard Operating Procedures
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TB	Tuberculosis
THAM	TromeThamine
TLR	Toll-like Receptor
TMG	Trial Management Group
TSE	Transmissible spongiform encephalopathy
TSC	Trial Steering Committee
VC	Vital Capacity
WIT	Warm Ischaemic Time
WLS	Withdrawal of Life Support

4. Responsibilities

Funder: NIHR Health Technology Assessment Programme is funding this study (funder's reference 10/82/01).

Sponsor: The Newcastle upon Tyne Hospitals NHS Foundation Trust will act as the sponsor for this study.

Chief Investigator: Professor Andrew Fisher will have overall responsibility for this study.

Trial Management: A Trial Management Group (TMG) will be appointed and will be responsible for overseeing the day to day progress of the trial. The day-to-day management of the trial will be co-ordinated by the Newcastle Clinical Trials Unit (NCTU). The NCTU will support the Chief Investigator in discharging sponsor-level activities which are delegated to him.

Principal Investigators: The Principal Investigators will have overall responsibility for the conduct of the study at a his/her trial site.

5. Protocol Summary

Short title:	DEVELOP-UK
Protocol version:	3.0
Protocol date:	24 August 2012
Chief Investigator:	Professor Andrew Fisher
Sponsor:	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Funder:	NIHR Health Technology Assessment programme
Study design:	**Non-randomised, non-inferiority observational study with an adaptive design**
Study Intervention:	Ex-Vivo Lung Perfusion (EVLP) of Donor Lungs
Primary objective:	To measure survival during the first 12 months after transplantation in recipients of EVLP assessed and reconditioned donor lungs (treatment group) compared to that of recipients of standard donor lungs (control group), in order to assess whether survival in the EVLP treatment group over that period is non-inferior to that in the standard control group
Secondary objectives:	To evaluate important early clinical outcomes and changes in quality of life (QOL) in the treatment and control groups in their first post-transplant year To assess, by statistical modelling, the survival benefit for waiting list patients of introducing EVLP technology into the UK lung transplant service, relative to the current service To determine if EVLP is a cost-effective intervention for the NHS to support as standard care within UK lung transplant centres in the future To explore the attitudes towards EVLP in patients awaiting lung transplantation and experiences of patients receiving EVLP reconditioned lungs
Primary outcome:	Survival during the first 12 months after lung transplantation
Number of study sites:	5
Study population/size:	Total sample size of 408 if the study continues beyond the interim analyses. Interim analyses to be performed after ⅓ and ⅔ of planned recruitment is reached
Study duration:	45 months (recruitment period 36 months)

6. Background

6.1 Study rationale

Respiratory diseases account for one in five deaths in the UK. Lung transplantation is the only realistic therapeutic option for selected patients with end-stage chronic lung disease and provides dramatic improvements in both survival and quality of life. In younger patients with life threatening cystic fibrosis lung disease, median survival after lung transplant now exceeds 10 years. Unfortunately, 20-30% of patients waiting for lung transplantation will die before a donor organ becomes available. Although a shortage of multi-organ donors contributes, the main problem is that the lung in the multi-organ donor is very susceptible to dysfunction and about 80% of potential donor lungs in the UK are deemed unusable for clinical lung transplantation. It has previously been suggested that in addition to promoting more organ donation, better use of existing organ donors is an important way in which to increase the numbers of lung transplants performed (1) and many centres worldwide have thus increased donor lung use by accepting more 'marginal' or 'extended criteria' donors. This however is not without risks to early post-transplantation outcomes (2). The major early cause of death after lung transplantation is primary graft dysfunction (PGD), a severe lung injury akin to acute respiratory distress syndrome (ARDS). Evidence that PGD has a major impact on survival comes from experience in several centres worldwide (3) and from the ISHLT where reported incidences of PGD are up to 25% with a 30 day mortality of 50% compared to <10% in those without PGD (4). There is, therefore, an urgent clinical need to safely increase the utilisation of donor lungs from the existing donor pool without negatively impacting on early survival after lung transplant.

Ex-Vivo Lung Perfusion (EVLP) is a novel technique in which unusable donor lungs which are functioning poorly or in which function is uncertain, can be assessed objectively and potentially reconditioned for safe use in clinical lung transplantation, thereby increasing the donor pool. Evaluation of human donor lungs in isolated perfusion circuits offers unique advantages as isolation of the lung may alleviate injurious factors associated with the donor or recipient haemodynamics, hormonal derangements and their pro-inflammatory milieu. This allows time for optimisation of the donor lung without the immediate risk associated with fully supporting the recipient. EVLP can also objectively identify lungs which are not suitable for transplantation either because poor function is due to irreversible damage or because pre-existing lung disease is identified in the donor lung. In this respect, EVLP may provide reassurance to potential recipients that 'marginal' or 'extended criteria' donor lungs that might have been previously considered unusable are acceptable for lung transplantation.

Approximately 25% of the world's experience with EVLP (17 out of approximately 65 cases as of June 2011) has been performed in the UK. Although initial experience is very promising, a large scale trial of the procedure is required to demonstrate its effectiveness in increasing lung transplant activity in a safe and cost effective way. The DEVELOP-UK study has been designed to address this urgent clinical need by assessing how effective EVLP assessment and reconditioning of donor lungs is at safely increasing UK lung transplant activity.

The overall objective of this study is to evaluate the clinical and cost effectiveness of the novel technique of donor EVLP in increasing UK lung transplant activity by allowing previously unusable donor lungs to be safely used in clinical lung transplantation. Furthermore DEVELOP-UK would allow the applicability of EVLP to lung transplant services in NHS to be determined. All of the objectives detailed below are measurable and will form part of the final study report.

6.2 Impact of Donor Lung Injury

The lung is very susceptible to injury in the critical care environment and the vast majority of donor lungs become unusable due to the dysfunction which develops in the hours or days leading up to the donors' demise. Marczin et al observed pulmonary and systemic inflammation in patients who

required mechanical ventilation for severe head injury. They also had characteristic changes in lung mechanics suggesting subclinical pulmonary inflammation before they became possible organ donors (5). Fisher et al have shown that acute inflammation in the donor lung (6) with elevated levels of interleukin-8 (IL-8) in donor bronchoalveolar lavage (BAL), is important in determining early outcomes after human lung transplantation (7). These observations have subsequently been reproduced elsewhere in the world (8). In addition, an imbalance between inflammatory interleukin-6 (IL-6) and anti-inflammatory interleukin-10 (IL-10) gene expression in donor lung predicts adverse early outcomes after human lung transplantation (9). These clinical observations have been modelled by Dark and colleagues using a rat model of brain-death induced donor lung injury and subsequent rat lung transplantation (10). Brain-death, together with trauma; infection; aspiration or transfusions, is now considered an important cause of donor lung inflammation and significant progress in understanding its pathophysiology has been made (11). Other animal models of lung transplantation have demonstrated that adenoviral gene therapy to upregulate expression of the anti-inflammatory cytokine interleukin-10 (IL-10) in the donor lung down regulates inflammation and improves function in the recipient animal after transplant (12,13,14,15). These observations suggest that attenuating the donor lungs' inflammatory response before implantation may improve early outcome after lung transplantation, and help to safely maximize lung use from the existing donor pool.

6.3 Assessment of Donor Lung Usability

Acceptance of potential donor lungs as usable for transplantation is a process that takes into consideration available donor history, subjective assessment of chest x-ray appearance, bronchoscopy and more exact physiological data such as arterial blood gases following oxygen challenge. Despite improvements in donor management practices, currently less than 20% of multi-organ donors provide lungs accepted for transplantation. The internationally accepted selection criteria of the "optimal donor" are primarily opinion, rather than evidence-based and their accuracy in determining the physiological status of the donor lung and predicting postoperative lung function is not optimal (16). Fisher et al have shown that current clinical donor lung assessment criteria are poor predictors of existing inflammation or infection in the donor lung (17) suggesting many donor lungs deemed unusable may be unnecessarily excluded. Ware and colleagues evaluated 29 pairs of unusable lungs by physiological, microbiological, and histological methods and concluded that as much as 40% of these lungs would have been potentially suitable for transplantation (18). Thus, there is urgent need to improve the donor lung selection process through more objective physiological assessment and EVLP can provide the platform to achieve this. In practice not all the unused donor cohort will be suitable donors as some will have absolute contraindications to lung donation, for others there will not be a suitable matching recipient on the waiting list. It is nonetheless suggested that EVLP could have the potential to increase availability of donor lungs for transplant by 50-100%. However the current clinical transplantation infrastructures would not cope with a near doubling in activity and in this study we are therefore aiming for a 30% overall increase in lung transplant activity.

6.4 Early Pathway Development

EVLP was first reported in a canine model in 1970 as a technique to assess the quality of the donor organ in animal models of lung transplantation. Subsequently porcine studies reported that maintenance of intact vascular function was achievable for up to 24 hours using EVLP and that functioning lungs could be obtained from DCD donors in a porcine model. The clinical EVLP technique was initially developed by Steen and colleagues in Sweden to assess lungs from DCD donors before transplantation. Their initial work in animal models was subsequently translated into the world's first successful clinical report in 2001 of a lung transplant performed using lungs from a DCD donor assessed by EVLP prior to successful transplantation (19). Further experimental work in human donor lungs demonstrated that assessment and reconditioning of unusable organs using EVLP could result in significant improvements in arterial oxygenation and pulmonary vascular

resistance (20). This led to the first clinical report in 2007 of reconditioning of an unusable donor lung prior to successful lung transplantation (21).

6.5 Clinical EVLP Experience Worldwide

Publication of the first successful lung transplantation using a reconditioned donor lung led to a rapid growth in interest in the EVLP technique. The Steen group described successful reconditioning and transplantation of 6 out of 9 donor lungs previously deemed unusable for transplant. All 6 survived the first 3 months and 4 of the 6 were alive and well 12 months after transplant (22). More recently, Keshavjee and colleagues in Toronto have modified the EVLP protocol significantly to include an acellular perfusate, a closed perfusion circuit and low perfusion pressures of no more than 40% of cardiac output and demonstrated lungs can be maintained for prolonged periods with this EVLP approach (23). This group have recently published their experience of the HELP study (24) performing EVLP on 23 donor lungs unacceptable for transplant that translated into 20 clinical lung transplants. Outcomes in this group were comparable to that achieved with standard transplants with a 15% incidence of Primary Graft Dysfunction (PGD) in the EVLP group and 30% in the standard transplant group (p=0.11).

The UK was the third country worldwide to perform a transplant using EVLP assessed and reconditioned donor lungs. The first case was performed by the Manchester group followed rapidly by the programmes in Harefield (25), Newcastle and more recently Cambridge. As of June 2011, UK activity totals 17 transplants performed with lungs that would not have been used without EVLP assessment and reconditioning. The 90 day survival in these 17 cases is 100% and 15 remain alive and well as of June 2011 (1 death at 9 months due to pneumonia and 1 death at 18 months due to rejection). When the Swedish and UK experience is added to the Toronto experience it suggests early survival is very good with 2 deaths within 90 days from over 65 EVLP transplants. The UK experience revealed the successful conversion rate during EVLP from unusable to usable donor organs was approximately 50% which is lower than that reported in the Toronto experience. This may represent the high proportion of DCD donors in the Toronto experience where EVLP was being used primarily for assessment rather than reconditioning.

International experience has since grown with case series now reported by the groups in Madrid, Vienna, Milan and Gothenburg with cases successfully transplanted with EVLP lungs recovered from uncontrolled and controlled DCD donors. The UK is in a unique position with 4 of its 5 adult centres having already developed clinical experience in EVLP. To date there have been no systematic studies powered to evaluate the effectiveness, safety and cost-effectiveness of EVLP performed anywhere in the world.

6.6 EVLP Biological Mechanisms of Action

There are a number of mechanisms by which the reconditoning effects of EVLP are believed to occur. These are outlined below:

Haemodynamic factors*:* Controlling the speed and pressure of initial reperfusion of the transplanted lung in animal models reduces the risk of developing PGD (26). The EVLP protocol allows initiation of controlled reperfusion after ischaemia and preservation and controlled perfusion throughout EVLP which is rarely available in routine clinical transplantation. This allows slow rewarming of lung tissue and incremental perfusion of pulmonary vasculature over a prolonged period of time with continuous limitation of pulmonary artery pressures and thereby arterial and capillary hydrostatic forces to prevent further pulmonary oedema. Conducting EVLP at equivalent to very low left atrial pressures helps further by limiting hydrostatic forces in postcapillary venules and capillaries.

Protective lung ventilation: Protective lung ventilation strategies are the standard of care for ITU management of injured lungs. However the need for hyperventilation in the management of head injury generally overrides this principle in potential lung donors and avoidance of hypercapnia may limit the use of these strategies in transplant recipients. EVLP therefore provides a unique opportunity to adopt ventilation strategies that reduce excessive mechanical stretch (low tidal volume) and oxidative stress (low FiO2) and to employ sustained Positive End Expiratory Pressures to overcome atelectasis without deleterious effects on systemic haemodynamics. Bronchial toilet with site-directed BAL limits ventilation-perfusion mismatch, so avoiding regional hypoxia with high PVR and parenchymal damage. Immediate results from Gram stains of BAL directs antibotic therapy with perfusion itself reducing microbacterial load (Karamanou et al, Abstract ISHLT Scientific Meeting 2010).

Perfusate related factors: One of the major mechanistic benefits of EVLP is the use of Steen solution as a high osmolarity, albumin and dextran rich perfusate. The solution can alter filtration forces to remove interstitial lung water and reduce pulmonary oedema. This may be responsible for the improved oxygenation observed between assessment in the donor and assessments during EVLP. In addition albumin may act as an antioxidant and dextran limits cell aggregation and microthrombi formation. The retrograde and antegrade perfusion during EVLP with use of a leucocyte filter in the circuit will also facilitate removal and prevent recirculation of intravascularly primed or activated leukocytes. Indeed, experimental models indicate reduced myeloperoxidase content of EVLP lungs which are a biomarker of neutrophil mediated responses.

Removal from the inflammatory donor environment: Another potential mechanism of lung reconditioning using EVLP may simply be the relocation of the donor organ from the sub-optimal, brain death environment in the donor. Eliminating the ongoing triggers of donor lung inflammation including the endogenous TLR ligands and activated donor leukocytes in a normothermic perfusion state may allow reduced inflammatory gene expression and restore protective anti-inflammatory mechanisms.

Opportunities for pharmacological, genetic and cell based therapies: Along with steroids, heparin and antibiotics, a potential future option may be supplementation of perfusate with cytoprotective pharmacological substances including vasodilators, antioxidants, cytokine blockers, established inhibitors of inflammatory pathways, fibrinolytics and immunomodulators. Such strategies may facilitate better reconditioning of the lungs to increase conversion rates to successful transplantation and long term survival. A genetic approach to improve cytokine balance has been shown to be beneficial in a large animal model of EVLP and transplantation and IL-10 gene therapy has been applied to human EVLP lungs (27). Similarly, a stem cell therapy approach via EVLP has been shown to improve acute lung injury in human lungs (28).

6.7 Rationale for Intervention (EVLP reconditioned lungs) and Control ('standard' donor lungs) Conditions

The experimental intervention in this study is use of EVLP assessed and reconditioned donor lungs for transplantation; the rationale for this intervention is described in 6.1 above. The control is use of standard donor lungs, i.e. without EVLP assessment and reconditioning, which represents current normal care within the UK lung transplant service.

This is a non-randomised study. The matching of potential donor lungs to potential recipients is dictated by a number of independent factors including donor and recipient size, blood group and, if applicable, tissue HLA matching. It is therefore not logistically possible to randomise recipients to receive either standard or EVLP donor lungs as part of the study. Furthermore, any attempt to randomly pre-allocate patients on the waiting list to an EVLP or standard group could give rise to a situation where a recipient may not be able to access a well matched donor organ because it did not fall into their pre-allocated group, which would not be ethically acceptable.

Lung donations from donors with brain death (DBD) and donors after circulatory death (DCD) will be considered in both arms of this study. The number of DCD donors is increasing year on year in the UK. Evidence has emerged that, when lungs from these donors are transplanted, outcomes in recipients are comparable to that achieved with lungs from DBD donors. However only a fraction of the UK DCD donors have their lungs used for standard transplantation. Frequently, there is either insufficient data available to be able to objectively assess the function of the lungs from DCD donors or there is a prolonged warm ischaemic phase after withdrawal of life support which renders the lungs unusable for standard transplantation. EVLP does however provide the potential to assess and potentially recondition lungs from DCD donors that cannot be used for standard transplantation.

An increase in the proportion of DCD donor lungs being used is anticipated as a direct result of the DEVELOP-UK study as DCD donors are often deemed unusable due to a lack of functional information about the organs and this is an indication for use of EVLP assessment. As the number of DCD donors increases it is likely that there will be more lungs from this cohort in the EVLP arm of the study than in the standard arm. This reflects the potential for EVLP to significantly increase the use of lungs from DCD donors. The proportion of DCD lungs that are currently being transplanted in the UK without EVLP, their quality and post-transplant outcomes will be collated before the start of the DEVELOP-UK study. This will permit an assessment of any changes in criteria for use, proportion and quality of DCD lungs by the end of the study. To ensure that the possible higher proportion of DCD donor lungs in the EVLP arm of the study does not bias the results, the donor type DCD or DBD will be used as co-variates in the multiple regression analysis of the primary and secondary outcome measures to determine their influence.

6.8 Risks and anticipated benefits for trial participants and society

There is a huge discrepancy between the supply of usable donor lungs and the number of patients with end stage lung disease who could potentially benefit from lung transplant surgery in terms of extended longevity and improved life quality. As a result, many patients perish on the waiting list before a suitable donor lung(s) becomes available. EVLP allows otherwise unusable donor lungs to be meticulously assessed and potentially reconditioned for successful transplantation. The study will also help us to better understand how to optimise use of lungs procured from DCD donors. This technology therefore has the potential to expand the donor pool and increase UK lung transplant activity thereby shortening time spent on the waiting list and reducing waiting list deaths.

The primary risk for the individual candidate is that, if in the EVLP arm, they could receive a lung or lungs that do not function well, but that risk also exists for donor lungs accepted by the current standard methods. Compared with standard criteria organs, it is not anticipated that EVLP will expose recipients to a different risk profile in terms of microbiological exposure, intensity of induction and maintenance immunosuppression or early post surgical complications.

Patients awaiting lung transplantation have severe, often complex morbidity and place a heavy burden on both health and social services. Data from the ISHLT registry clearly demonstrate that nearly 80% of successful lung transplant recipients have no or little functional limitation and around 40% return to either full or part-time employment, the rest being close to or over retirement age. Less than 20% require inpatient treatment related to their lung disease post hospital discharge following the transplant procedure. Thus, by increasing the numbers of successful transplants, EVLP may help reduce the UK health and social care costs of patients awaiting lung transplantation. Furthermore, the trial will assess the economic impact of using EVLP reconditioned lungs. It will allow policy makers to balance these costs against the benefits of increased donor utilisation and reduced waiting time mortality. The study will help determine if EVLP is a cost-effective use of tax-payers' money and an intervention applicable to NHS lung transplant services.

6.9 Patient population to be studied

This is a UK national multi-centre study involving all five officially designated NHS lung transplant centres:

Freeman Hospital, Newcastle Upon Tyne; Harefield Hospital, London; Papworth Hospital, Cambridge; Wythenshawe Hospital, Manchester; Queen Elizabeth Hospital, Birmingham

These five centres provide all adult lung transplant activity to potential recipients with end-stage chronic lung disease in England, Scotland, Wales and Northern Ireland.

The target population for the study will be all adult patients, aged 18 years and over, with advanced lung disease already accepted (at study inception) onto an active lung transplant waiting list in one of the five UK centres plus any new adult patients that are added to the active waiting list during the course of the study. The network coverage means all 230-240 patients awaiting lung transplantation in the UK at any one time, will have the opportunity to take part in the study and pilot experience suggests over 90% will consent to take part. The study will in no way affect how potential lung transplant recipients are assessed or selected or the timing of when they are added to the active transplant waiting list.

As a non-randomised, non-blinded study, it is important that the potential for bias in the selection of recipients to receive donor lungs from the EVLP or standard arms is considered and carefully monitored. There is however no *a priori* reason to expect a systematic difference to exist in characteristics between the recipients in the two arms of the study. This is because the donor-recipient match is established (see 6.7 above) before the clinical decision on the usability of the donor lungs is made, meaning that recipient selection will not be influenced by whether EVLP conditioned or standard lung donation occurs. In particular there is no evidence to suggest that sicker recipients, whose transplant might be seen as more urgent, will be more likely to receive EVLP reconditioned lungs than standard lungs.

Only when donor lungs are available that have more than one potentially matching recipient will urgency be taken into account by the transplant centre. This scenario is likely to happen as frequently in the standard transplant arm as in the EVLP arm. The two arms of the study will be monitored carefully to ensure no systematic differences exist in the recipient characteristics. Additionally, recognised co-variables that are known from the International Registry to influence outcomes after lung transplantation will be adjusted for in the statistical analysis. Our pilot experience of transplants performed using EVLP reconditioned lungs across the UK centres has indicated that patients with a range of disease indications, ages, disease severity and both single and bilateral transplants have been included, reflecting the variability that exists on the lung transplant waiting list.

Study objectives

6.10 Primary Objective

The primary objective is to measure survival during the first 12 months after transplantation in recipients of EVLP assessed and reconditioned donor lungs (treatment group) compared to that of recipients of standard donor lungs (control group). We aim to assess if survival in the EVLP treatment group over that period is non-inferior to that in the standard control group. The study is therefore powered to address this primary objective.

6.11 Secondary Objectives

The secondary objectives are to evaluate important early clinical outcomes and changes in quality of life (QoL) in the treatment and control groups in their first post-transplant year. The patients' clinical course in the ITU immediately post-transplant and subsequently in their first post-transplant year will be captured by collection of well validated outcome measures. The aim is to assess if the early clinical course and impact on QOL following receipt of EVLP donor lungs is comparable to that achieved with standard donor lungs and also the study aims to assess the survival benefit for waiting list patients of introducing EVLP technology into the UK lung transplant service, relative to the current service, by use of statistical modelling.

In addition, the full economic impact of using EVLP reconditioned lungs will be assessed, allowing policy makers to consider these costs in comparison with benefits of increased donor utilisation and reduced waiting list mortality. We aim to determine if EVLP is a cost-effective intervention for the NHS to support as standard care within UK lung transplant centres in the future.

To gain understanding of the potential impact of EVLP provision to service users, we will explore the attitudes towards EVLP in patients awaiting lung transplantation and experiences of patients receiving EVLP reconditioned lungs in a qualitative interview sub-study.

The DEVELOP-UK study will provide a unique opportunity to better understand the donor and procedure-related clinical determinants of successful or failed EVLP donor lung reconditioning. Objective clinical and physiological indices in the donor lungs before and during EVLP will therefore be correlated with the decision whether to accept the donor lungs for transplant and with clinical outcomes in recipients of EVLP donor lungs.

To add significant value to the DEVELOP-UK study, standardised protocols for bronchoalveolar lavage (BAL), perfusate and lung tissue sampling during EVLP and subsequent storage have been developed. The collection and storage of samples during EVLP is part of the DEVELOP-UK study and will allow complementary mechanistic studies of EVLP to be performed from this dataset. The laboratory based mechanistic work however will happen out with the main study and will be funded from non-HTA funding sources.

7. Study Design

This is a multi-centre, unblinded, non-randomised non-inferiority observational study with an adaptive design to evaluate the clinical and economic effectiveness of ex-vivo lung perfusion (EVLP) to assess and recondition donor lungs for transplantation compared with standard lung transplantation. The study also includes an embedded qualitative sub-study.

7.1 Primary outcome measure

Survival during the first 12 months following lung transplantation has been chosen as the primary outcome measure in the study. It is a robust, well recognised, clinically relevant outcome which is used in the Royal College of Surgeons national audit of UK cardiothoracic transplant activity and in the ISHLT registry. A dichotomous outcome such as survival to 30, or 90, days (yes/no) would be less informative, and omit valuable information about potentially differing survival patterns between the two study groups.

7.2 Secondary outcomes

The secondary outcome measures in this study are all important clinically relevant patient centred outcomes which are influenced by the effectiveness of lung transplantation and contribute to the healthcare costs and impact on quality of life (QoL).

Primary Graft Dysfunction (PGD) is a clinical entity that reflects the development of early acute lung injury after lung transplantation. PGD was first defined by a working group (which included a number of the study investigators) of the ISHLT in 2005. Its severity is graded between 0 and 3 and it is measured at 0-6, 24, 48 and 72 hours after lung transplantation. The grade is determined by the degree of gas exchange impairment and by the presence of infiltrate on the post-operative chest x-ray. The PGD grade has been validated in both retrospective and prospective studies and presence of PGD grade 3 at 72 hrs is associated with a reduced early survival. A full PGD score will be determined for all patients in the study.

The duration of invasive ventilation and duration of ITU stay after lung transplantation will be collected on all study participants and will provide a valuable surrogate of a range of complications in early post-operative course. In addition **the duration of hospital stay** before first discharge home will give a good indication of how effectively the patient is rehabilitating after their lung transplant. These measurements will also provide useful information on health resource utilisation for economic evaluation.

The presence of specific post-operative complications will be collected as secondary outcome measures. These will include any **anastomotic complications** scored using a recognised and validated system (Couraud Classification see Appendix 5) including dehiscence or stricture requiring dilatation or stent placement; episodes **of infection** requiring treatment with or without associated hospital admission during the first year; episodes of **acute rejection** of ISHLT grade A2 or higher and B1 or higher or clinically diagnosed requiring treatment during the first year.

Details of **lung function** measurements by Forced Expiratory Volume in 1 second (FEV_1) and Vital Capacity (VC) at 1, 3, 6 and 12 months post transplant will be collected to demonstrate changes in lung allograft function in the first year. Data on **chest x-ray appearance** at the same time points as lung function will be collected to look for any persistent abnormalities such as effusions, cavitations or scarring from the time of transplantation.

Patient **survival rate at 90 days** post transplantation will also be collected as an internationally recognised outcome measure in lung transplantation that can be benchmarked against outcomes reported in UK and international (ISHLT) registries.

An assessment of **quality of life (QoL)** using SF-36 will be collected while study participants are waiting for transplant and at 90 days and 1 year post transplantation allowing comparison to QOL measured on the waiting list. The QOL scores will allow health utility scores to be determined using SF-6D as part of the economic evaluation.

Additional perioperative physiological data will be collected in selected centres from lung transplant recipients in the ITU environment. These measurements will complement the mechanistic studies being performed in parallel to DEVELOP-UK by providing additional clinical correlates. These include an assessment of extravascular lung water (EVLW) as a measure of lung permeability and airway and tissue mechanics. EVLW will be measured using the PiCCO system (PULSION Medical Systems, Munich, Germany), which uses a single indicator transpulmonary thermodilution method and is a licenced device in standard clinical use in ITU environments. In addition, lung mechanics will be evaluated by measures of static and dynamic compliance and respiratory impedance using the low-frequency forced oscillation technique via the ITU ventilator.

7.3 Definition of end of study

A pragmatic decision has been made to close data collection 6 months after the last patient is recruited even though there will be outstanding primary and secondary outcome measures (survival over 12 months, QOL) from a few patients. The primary outcome data (survival over 12 months) will be available for about 85% of the patients by that time point. Survival data from the remaining 15% will be censored at the time of closing the study and will therefore still contribute to the final analysis. This approach will lead to only a very minor reduction in power, which will remain at 80%.

8. Study Population

This is a UK national multi-centre study involving all five officially designated NHS lung transplant centres: Birmingham, Harefield (London), Manchester, Newcastle and Papworth (Cambridge). These five tertiary centres provide all adult lung transplant activity to potential recipients with end-stage chronic lung disease in England, Scotland, Wales and Northern Ireland.

The target population for the study will be all adult patients, aged 18 years and over, with advanced lung disease already accepted (at study inception) onto an active lung transplant waiting list in one of the five UK centres plus any new adult patients that are added to the active waiting list during the course of the study recruitment period.

8.1 Inclusion criteria (trial)

- Male or female patients
- Adult patients (aged over 18 years)
- Patients already on or added to the active waiting list for first lung transplant while the DEVELOP-UK study is in its recruitment phase
- Patients providing informed consent for participation in the DEVELOP-UK study at the time of study commencement or time of listing for transplant
- Patients re-confirming informed consent for the DEVELOP-UK study on the day of lung transplant*

(* If Informed Consent Form was signed on the day of transplant re-confirming consent is not required).

8.2 Exclusion criteria (trial)

- Patients aged less than 18 years
- Patients listed for lung re-transplantation
- Patients listed for heart-lung transplantation
- Patients listed for live donor lobar transplant
- Patients not in possession of patient information sheets for the DEVELOP-UK study prior to the day of lung transplant
- Patients not re-confirming consent for the DEVELOP-UK study on the day of lung transplant*
- Patients in the ITU requiring invasive ventilation, ECMO or Novalung support
- Patients enrolled in Trials within the preceding 12 months (please discuss with principal and chief investigators before exclusion on this basis)

(* If Informed Consent Form was signed on the day of transplant re-confirming consent is not required).

8.3 Criteria for lung selection, donation and transplant

8.31 Absolute contra-indications to all solid donor organ use for standard transplant: Donation after Brain Death (DBD) (NHSBT Guidelines)

- Age >85 years
- Cancer with evidence of spread outside affected organ (including lymph nodes) within 3 years of donation (however, localised prostate, thyroid, *in situ* cervical cancer and non-melanotic skin cancer are acceptable)
- Active melanoma
- Choriocarcinoma
- Active haematological malignancy (myeloma, lymphoma, leukaemia)

- Definite, probable or possible case of human TSE, including CJD and vCJD, individuals whose blood relatives have had familial CJD, other neurodegenerative diseases associated with infectious agents
- TB: active or within 6 months of treatment*
- Malaria: if not fully treated*
- Meningoencephalitis for which no infection has been identified*
- HIV disease (but not HIV infection)

(*****in exceptional cases)

8.32 Absolute contra-indications to all solid donor organ use for standard transplant: Donation after Cardiac Death (DCD) (NHSBT Guidelines)

- As above but age >80 years

8.33 Absolute contra-indications to donor lung use for standard transplant or for EVLP

- Donor age >65 years
- Donor HIV positive or other contra-indicated infection risk eg Hepatitis B or C unless being used for a HIV, Hepatitis B or C positive recipient
- Chest trauma with extensive bilateral lung contusions
- Convincing evidence of bilateral pneumonic consolidation on inspection
- Pre-existing structural lung changes (e.g. emphysematous or multiple large bullae)
- Previous complex intra-pleural thoracic surgery or dense adhesions prohibiting safe lung procurement
- Confirmation of malignancy within 5 years (excluding central nervous system malignancies)

8.34 Criteria for Standard Transplant

Using Donation after Brain Death (DBD) donor lungs

- Satisfactory Chest X-ray reviewed by retrieval surgeon
- Systemic arterial PO_2 > 35-40 kPa on 100% FiO_2 and 8cm H_2O PEEP
- Selective Pulmonary Vein (PV) Gases >30kPa on 100% FiO_2 and 8cm H_2O PEEP
- Peak airway pressure < 30 cmH_2O
- Bronchoscopy – no severe inflammation of the airway, or recurrent secretions in the distal airway after adequate bronchial toilet
- Easily recruited atelectasis
- Satisfactory deflation test on disconnecting endotracheal tube
- Satisfactory palpation of the lung to exclude undetermined masses, nodules or gross oedema
- Satisfactory inspection of the lung after administration of the preservation flush and procurement

Using Donation after Circulatory Death (DCD) donor lungs

- Satisfies criteria as for standard DBD donor lungs (if information available)
- DCD Donors from Maastrict Category 2, 3 or 4
- Systemic arterial PO_2 > 40 kPa on 100% FiO_2 and 8 cmH_2O PEEP, or equivalent FiO2:PaO2 within 12 hours
- Warm ischaemic time (WIT) < 30 minutes
- (WIT starts when donor systolic BP < 50 mmHg and / or O_2 sats < 70%)
- Withdrawal of life support (WLS) time < 120 minutes

8.35 Criteria for EVLP Assessment and Reconditioning – Using DBD or DCD lungs
Any one or more of the following:

- Warm Ischaemic Time (WIT) > 30 minutes for DCD donors but < 60 minutes
- Chest X-ray findings prohibitive to standard transplantation

- Systemic arterial PO_2 < 35-40 kPa and / or selective PV gas < 30 kPa on 100% FiO_2 and 8 cmH_2O PEEP
- History of aspiration with bronchoscopic inflammation/soiling of the airway, or recurrent but not prohibitive secretions in the distal airway after adequate bronchial toilet
- Difficult to recruit atelectasis
- Sustained peak airway pressure > 30 cmH_2O
- Unsatisfactory deflation test on disconnecting ET tube
- Unsatisfactory palpation of the lungs identifying undetermined masses, nodules or gross oedema
- Deterioration or cardiac arrest in the donor prior to retrieval such that uncertainty over assessment remains
- Unsatisfactory inspection of the lung after administration of the preservation flush and procurement
- Logistical reasons that will extend donor lung ischaemic time >10-12hrs and prevent donor organ use, such as:
    - Viral studies awaited
    - HLA compatibility studies
    - Pathology assessment of indeterminate mass in any donor
    - Awaiting recipient admission

8.36 Criteria for Transplant after Successful EVLP Assessment and Reconditioning

- Any DBD or DCD donor lungs meeting previously stated criteria for standard transplant
- Pulmonary artery pressure <20mmHg, whilst achieving at least a target flow of 40-60% of a calculated donor flow index of 3 litres/min/m^2
- Oxygen capacity shown by deltaPO_2 of >40kPa (perfusate LA PO_2 – perfusate PA PO_2) / FiO_2
- Selective PV gas > 30 kPa on 100% FiO_2 and 5 cm H_2O PEEP
- Stable or improving lung compliance and stable or falling lung resistance
- No pulmonary oedema build-up in the ET tube
- Satisfactory assessment on inspection and palpation
- Confirmed re-consent of potential matched recipient to receive an EVLP reconditioned lung*

(* If consent was given on the day of transplant re-consent is not required)

8.37 Criteria for Failed EVLP Assessment and Reconditioning: transplant will not proceed

- Any DBD or DCD donor lungs not meeting stated criteria for standard transplant
- Not satisfying criteria for transplant after successful EVLP assessment and reconditioning

8.4 Inclusion criteria for interview sub-study

- All patients who are eligible for the DEVELOP-UK trial
- Patients at Newcastle Hospitals NHS Foundation Trust and Royal Brompton and Harefield NHS Foundation Trust only
- All patients who consent to the DEVELOP-UK trial as a whole and the interview sub-study specifically (regardless of whether they receive a transplant)

8.5 Exclusion criteria for interview sub-study

- All patients who have consented to the DEVELOP-UK trial from Manchester, Papworth and Birmingham sites

9. Screening, Recruitment and Consent

All adult patients, aged 18 years and over, with advanced lung disease already accepted (at study inception) onto an active lung transplant waiting list in one of the five UK centres plus any new adult patients that are added to the active waiting list during the course of the study are potentially eligible for this study.

9.1 Lung Recipient Pathway Pre and Post Transplantation

Patients referred to any of the 5 participating sites for consideration of lung transplantation over the course of the study recruitment phase will undergo a period of standard clinical assessment. Those deemed eligible for and who consent to lung transplantation will be added to the active lung transplant waiting list (those on the transplant list at the time of study inception will already have been through the same assessment process).

At the time of listing for transplant, patients will be offered the opportunity to take part in the DEVELOP-UK study. In addition, at the time of study inception, any patient who is already on the active lung transplant list will also be offered the opportunity to take part in the DEVELOP-UK study. The consent process will be performed in accordance with NRES guidance as described below. As the period of waiting for lung transplantation can vary widely and can commonly exceed 12 months, it will be necessary to reconfirm consent for the study at the time when a potential donor lung(s) becomes available and the study participant is called in for possible transplantation. However, if consent form was signed on the day of transplant reconfirmation of consent is not required.

Whether the patient is to receive a donor lung that has undergone EVLP assessment and reconditioning or a standard donor lung will be explained on the day of transplant. Patients will either receive standard donor lungs direct from a donor (standard transplant, control arm), or donor lungs after EVLP assessment and re-conditioning (treatment arm) according to donor organ/recipient matching.

Transplanted lungs, whether ‘standard’ or EVLP reconditioned, always remain vulnerable to the possibility of rejection and one of the main risk factors is low immunosuppression levels. For this reason, patients are heavily counselled prior to being accepted onto the transplant list about the necessity of absolute concordance with their treatment and in attending all arranged post-transplant follow-up. As a result, during the multi-disciplinary pre-transplant assessment, a considerable amount of time is spent explaining this aspect of care to the patients. If despite these attempts there remains evidence of non-compliance with treatment these individuals would not usually be offered the option of transplantation.

9.2 Lung Recipient Consent

Informed and voluntary consent will be obtained via an iterative process, providing adequate time of not less than 24 hours, at initial consent (see below) for consideration and discussion of the clinical and research aspects of the study and subsequently re-consent on the day of possible transplant. If, however, consent form was signed on the day of transplant re-consent is not required. Consent for DEVELOP-UK study participation will be sought separately from the standard consent for lung transplant surgery.

No additional screening procedures, over and above those necessary to determine eligibility and suitability for lung transplant, are required to determine eligibility for the trial element of DEVELOP-UK. Therefore all adult patients being considered for lung transplant that satisfy the inclusion criteria will be approached to take part in the DEVELOP-UK study.

Patients waiting for transplantation are desperately sick, very vulnerable and grasping at any lifeline. Securing genuinely informed consent is therefore an important consideration. The initial consent process will take place well ahead of the time of transplant (i.e. either at inception of the study for those already on the transplant list, or at the time of listing for transplant for those added to the active transplant list during the course of the study) and the stressful environment that this generates.

Consent will be taken by the local PI or a member of the study team with appropriate designated responsibility on behalf of the local PI. In the consent process, care will be taken not to unjustifiably inflate hope of a shorter waiting time for transplantation as a result of EVLP being available. A clear definition of what constitutes an unusable donor lung in the study will be explained; definitions of acceptability of lungs for standard transplantation and for transplantation after EVLP will be standardised across all centres. Patients will be offered firm reassurance that if donor lungs do not improve sufficiently after EVLP reconditioning to satisfy acceptability criteria they will not be used. Any potential recipient who decides not to participate in the DEVELOP-UK study will have equal access to donor lungs for standard transplant. Those choosing not to give consent will not be obliged to give a reason but if they chose to provide a reason this will be recorded in an anonymised way to inform the TSC.

Additional informed consent, using a separate participant information sheet and consent form, will be sought from the subset of patients approached to take part in the qualitative interviews; lack of consent to take part in this element of the study will not preclude participation in the main study.

For both the main study and the qualitative sub-study, if a potential participant has the capacity to consent for him/herself, but is unable to provide written consent because of visual or motor impairments, or literacy problems, oral informed consent will be taken in the presence of an independent witness (who will initial, sign and date the consent form on the participant's behalf).

Consent of patients on the active lung transplant waiting list at study commencement:

1. Eligible patients already on the active waiting list for lung transplantation will be sent a letter of invitation to participate in the DEVELOP-UK study. This will contain the main study patient information sheet (PIS) and an expression of interest (EOI) form.
2. This letter will be followed by a telephone call within one week by one of the research team to enquire about their willingness to take part and to answer any questions they may have after reading the patient information sheet.
3. The EOI form will ask them to declare whether or not they express an interest in taking part in the main study and also their willingness to be contacted about the interview study.
4. The completed EOI form will be returned to the transplant centre by post and the patients' response recorded on the transplant waiting list.
5. Those expressing interest in participating in the interview study will be subjected to purposeful sampling and identified patients will be contacted directly by the interview team and sent a more detailed PIS about the interview study.
6. Patients expressing interest in participating in the main study will have full informed consent taken by the PI or their designated deputy from the research team when they attend a clinic appointment for standard clinical review at the transplant centre.
7. If a patient is deemed too unwell to travel to the transplant centre for clinical review due to the severity of their lung disease and the associated risks of that journey but still wishes to enrol in the study then 2 options are available to obtain full consent:
    a. The patient may be seen in a local satellite lung transplant clinic where full informed consent will be taken (Belfast, Edinburgh and Glasgow).
    b. The patient will sign their full informed consent when called into the transplant centre for a potential lung transplant.
8. All participants who have signed an EOI form or full consent before the day of transplant will be re-consented on the day of a potential lung transplant at the transplant centre. Consent in this group on the day of transplant will be by use of the full consent form for those patients

only completing an EOI form previously or by use of the consent to continue form for those previously signing a full consent form.

Consent of patients added to the lung transplant waiting list after study commencement:

1. Patients attending the transplant centre for formal lung transplant assessment will be informed about the DEVELOP-UK study during their assessment visit and provided with the main study patient information sheet and any questions they have about the main study will be addressed.
2. Once a decision has been made on their suitability to be added to the waiting list and they have signed clinical lung transplant consent then they wil be asked about their willingness to participate.
3. Full informed consent will be taken face to face by the PI or their designated deputy from the research team. This process may occur in three scenarios:
    a. As an in-patient in the transplant centre at the end of their formal assessment visit.
    b. As an outpatient in a satellite lung transplant assessment clinic.
    c. As an outpatient if the patient returns to the transplant centre for clinical review after their assessment visit.
4. Those expressing interest in participating in the interview study will be subjected to purposeful sampling and identified patients will be contacted directly by the interview team and sent a more detailed PIS about the interview study.
5. All participants who have signed full informed consent before the day of transplant will be re-consented on the day of a potential transplant at the transplant centre.

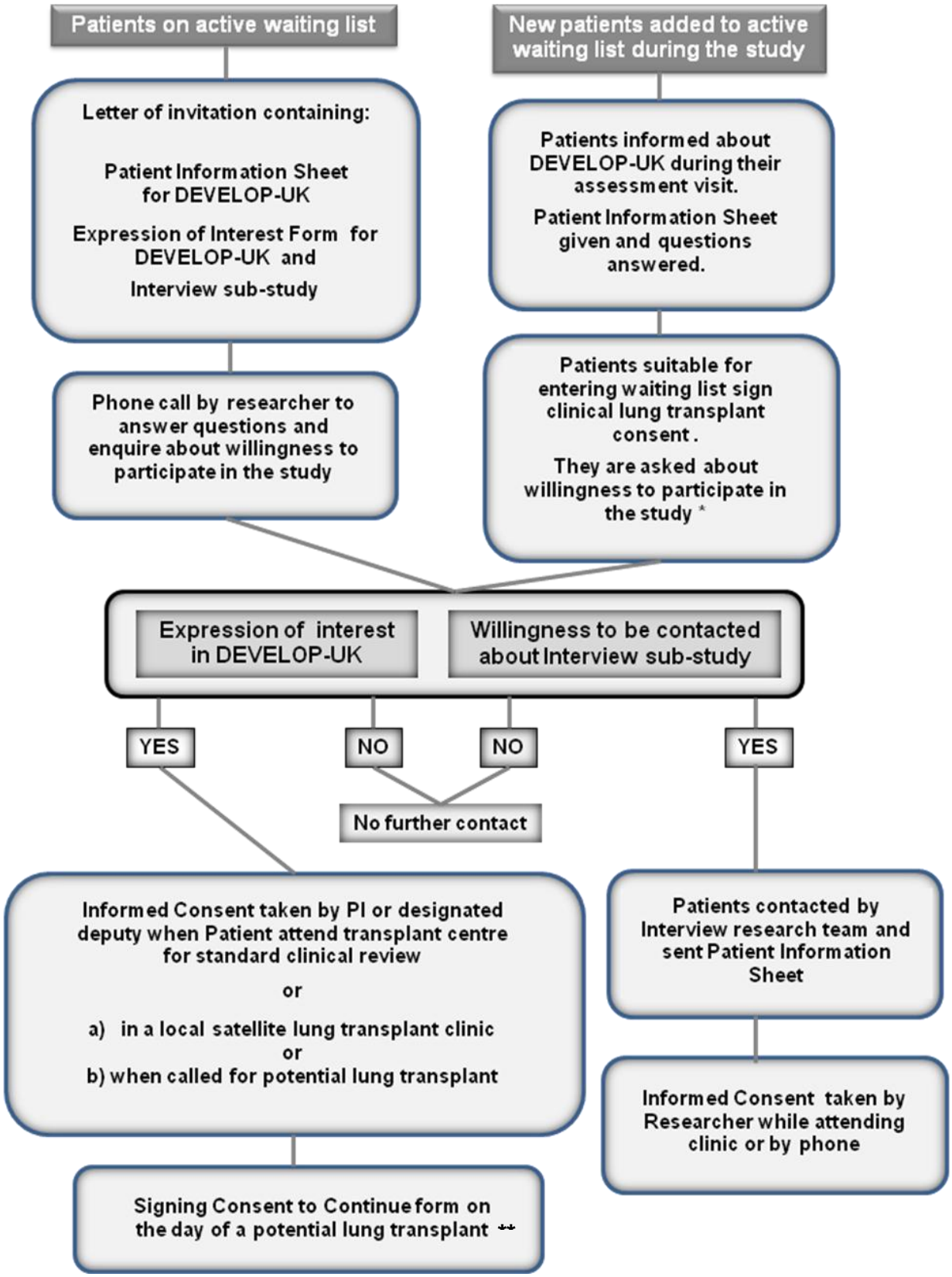
We do not anticipate that any potential study participants will lack capacity to consent on initial recruitment to the study or at the point of reconfirming consent at the time of a donor lung becoming available. It is, however, possible, though unlikely, that they could lose capacity over the follow-up period. For example, if as a result of transplant surgery any participant were to lose capacity temporarily or permanently such as by requiring prolonged ventilation on the ITU or by suffering a stroke, we will aim to continue to collect outcome measures in relation to such patients, working with personal or nominated consultees and in line with the requirements of the Mental Capacity Act. We will not seek separate written consent from nominated consultees in the event of loss of capacity as this scenario will be included in the initial participant consent form and they will be specifically asked to give consent for continued collection of observational data as part of the study if they lose capacity after transplantation. As much of the data in the follow-up period is observational, its collection will not impact on the standard care that any participant that has lost capacity would receive.

The original signed consent form and re-consent form will be retained in the Investigator Site File, with a copy in the clinical notes and a copy provided to the participant. The participant will be asked to consent explicitly to their GP being informed of their participation in the trial element of the DEVELOP-UK study.

The right to refuse to participate without giving reasons will be respected.

Due to the small subject population, the information sheet and consent form for the study will be available only in English. Interpreters will be arranged for all visits of patients who require them either for verbal translation or for deaf subjects wishing to take part in the study, via local NHS arrangements. Qualified interpreters will be used to explain the consent form and information sheet, and great priority will be placed on finding the most direct communication.

Lung Recipient Consent Process



* Patients added to the waiting list during the study may sign the informed consent without need for expression of interest form

** If Informed Consent Form was signed on the day of transplant signing Consent to Continue Form is not required.

9.3 Donor Next of Kin Consent

Consent for potential donor lungs to be used for lung transplantation will be obtained from the donor next of kin at the donor hospital by the specialist nurses for organ donation (SNODs) employed by NHSBT. This process is standardised nationally and will be performed completely independently of the DEVELOP-UK study.

If standard consent for lung donation is granted, the SNODs will additionally ask the next of kin for generic research consent which is a standard part of the donor consent form. This will allow the study team to collect and store samples from the donor lung before and after EVLP as described elsewhere in the protocol for parallel mechanistic studies even if the donor lungs are not deemed transplantable after EVLP.

If however the donor next of kin do not provide generic research consent then only clinical data measured during the EVLP process will be collected and used in the study and no lung tissue samples will be taken for mechanistic work. This would in no way compromise the delivery of the primary and secondary endpoints of the study.

10. Study Intervention Details

10.1 Experimental Intervention

The experimental intervention is ex-vivo lung perfusion (EVLP). EVLP is performed outside the donor or recipient body by connecting the lungs to a “modified” heart-lung bypass circuit which warms the lungs to body temperature and pumps the specialised nutrient solution or 'perfusate' through them. Following slow rewarming to 32°C, the lungs are ventilated with oxygen by connecting them to a standard ITU ventilator. EVLP provides the opportunity to carefully assess donor lung function including gas exchange ability over a number of hours before making a decision on their usability for transplantation.

When a lung suitable for potential transplantation becomes available, the NHSBT zonal organ retrieval team will be dispatched to the donor hospital to further assess the donor lungs. After careful assessment a decision will be made using the donor lung criteria (detailed above) as to whether the lungs can be used immediately for standard transplantation, should undergo EVLP assessment and reconditioning or are contraindicated for transplantation.

Donor Lung Procurement

The standard lung procurement procedure will be followed for donor lungs to be used for EVLP in the study. The organs are ante-gradely flushed with supplemented (3.6% THAM 3.3 mls, 0.6 ml CaCl +/- 2.5 mls Prostacyclin / litre) Perfadex®, the first one litre at room temperature, the rest at 4^{o}C. A minimum volume of 60ml/Kg will be given. After the antegrade dose, 200ml will be given down each pulmonary vein as a final retrograde flush. An adequate portion of main pulmonary artery (PA), left atrial cuff and particularly at least 4cm of trachea will be taken by the retrieval surgeon. A piece of aorta will be required to extend a deficient main PA (divided in close proximity to the bifurcation) to allow for successful cannulation and bilateral perfusion.

Study Protocol for Ex-vivo Lung Perfusion

The study team have elected to use the Vivoline® system for the study which is a semi-automated EVLP circuit housing the bypass pump, oxygenator/deoxygenator, perfusion reservoir and the perfused organ in a small contained unit. The system is used with a disposable lung set (DLS) containing all the necessary consumables for each EVLP run. The study EVLP protocol is based on a hybrid of the Toronto General Hospital and Lund University Hospital EVLP approaches. A simplified version of the protocol is provided below (detailed SOPs are in place for each element).

Please refer to the most current DEVELOP-UK ex-vivo lung perfusion Standard Operating Procedure for the most up to date technical aspects of EVLP conduct during the study.

Composition of the EVLP Circuit

EVLP will be performed in a suitably designated clinical area that fulfils the necessary infection control precautions. In most cases this will be in an operating theatre but it could be in an air-locked ICU cubicle with operating theatre standard positive pressure ventilation. Equipment required in addition to the Vivoline® system includes an ICU standard ventilator that can measure tidal volumes, lung compliance and resistance airway pressure, piped oxygen and a 93% nitrogen/7% carbon dioxide gas mixture. Staff supporting each EVLP run will include the clinical research fellow; surgical fellow or supervising consultant; anaesthetist or ODA, however there is also the option of providing a perfusionist and scrub nurse by individual centres to run the EVLP circuit for up to 4 hours.

Perfusion Strategy

Priming: The EVLP circuit is primed with 2.5L acellular Steen Solution™ that contains human serum albumin and dextran in an extra-cellular type electrolyte composition solution containing a low concentration of potassium. Packed red cells will not be added. The prime solution is supplemented with 10,000iu heparin, 20U Actrapid, 1g methylprednisolone and antimicrobials as

directed by donor cultures or as default by 50mg of Amphotericin B and 1g Meropenem (if there is no documented allergy to ß-lactams). Following analysis of the perfusate (blood gas machine), 3.0 mmol THAM, (approximately 1 ml of a 40% THAM solution) for each minus unit in gas machine measured base deficit. Run another perfusate sample after 10 minutes and correct with more THAM if required. Run priming for at least 15 minutes and re-check perfusate before the lung is connected.

Reconditioning: Surgical dissection is performed to allow placement of the donor lung onto the EVLP circuit (Vivoline®) in a covered organ bath that is devised to maintain humidity. Cannulation of the main pulmonary artery is with a quick-fix pre-fashioned cannula (aorta). The left atrium is left open and visualised to ensure a smooth flow of perfusate. A checklist between the surgeon, Vivoline circuit operator (perfusionist) and anaesthetist is performed prior to perfusion of the organs taking place. De-airing of the circuit (with the shunt open) is performed at a flow of 0.5L / minute until the circuit is fully de aired. Set the pressure to maximum 15 mmHg and the flow maximum to calculated target flow of 40-60 % of donors calculated cardiac index of 3.0. There should be a gradual and automatic increase in flow as the temperature rises. Flow should be carefully documented and in keeping with protective strategies for prolonged perfusion protocols. The EVLP circuit is maintained for a minimum of 60 mins up to a maximum of 240 minutes with both continuous data monitoring and hourly clinical assessments. During perfusion, Steen Solution™ perfusing the circuit and lungs will not be replaced. 3.6% Tham is administered to the Steen Solution™ during perfusion as indicated by base deficit values. Aim for a pH > 7.2 – 7.3, otherwise possible perfusate exchange can be considered.

Ventilation Strategy
Where possible the trachea remains clamped prior to insertion of a quick-fix ventilation tube that is secured in place. This prevents collapse of the lungs and development of atelectasis. As the perfusate is gradually increases to target flow, the lungs re-warm from storage temperature to 32°C (remaining clamped from the time of retrieval, partially inflated at 50% FiO_2), at which point ventilation is started. The lungs are carefully inflated by hand ventilation to reduce atelectasis and mechanical ventilation commences with protective ventilation strategies including low tidal volume (6-8ml/kg) and appropriate PEEP (5-8 cmH_2O) to avoid mechanical stresses and hyperinflation. The aim is to maintain an airway pressure below 25 mm Hg, prevent lung collapse and supply 21% FiO_2 to avoid oxygen toxicity. When set temperature is reached (36 – 37 °C) run a perfusate sample on the gas machine before entering the evaluation phase, PO_2 should be >40 kPa and pCO_2 <6 kPa to change into evaluation.

Assessment Strategy
The function of the donor lungs undergoing EVLP will be assessed formally initially once re-warming is complete and target perfusion flow established. The EVLP circuit will be continued for 120 to 240 minutes, maintaining a Vivoline® system measured PAP of < 20-25mmHg with target flow, with both continuous data monitoring and hourly clinical assessments* (ET tube oedema, palpation, deflation, endobronchial evaluation) complementing the evaluation phase until a decision on suitability of the lungs for transplantation is reached. Disconnect the oxygen prior to evaluation. Once the perfusate is deoxygenated, standard recruitment manoeuvres are performed and the FIO_2 is increased from 21% to 100%. Blood gas analysis to assess venous and arterial pO_2 values will be performed 15 minutes after FIO_2 is increased to 100%. Following the decision to proceed to transplantation, the lungs are cooled and maintained in topical Steen solution at 4 - 8 °C on the circuit (preservation phase) until ready for transplant. Ventilation is stopped at 32°C, partially inflated, 50% FIO_2. At the start of cooling, the recipient is moved to the anaesthetic room in preparation for lung transplantation.

Sample Collection, Processing and Storage
Collection and storage of biological samples from donor lungs is limited to those donor lungs exposed to EVLP assessment and reconditioning in the intervention arm and no samples will be collected from standard donor lungs in the control arm in the DEVELOP-UK study.

All samples will be processed at the study site according to the standard operating procedures included in the study laboratory manual and described briefly below. Samples of bronchoalveolar lavage, perfusate and frozen lung tissue will be initially stored in a dedicated DEVELOP-UK -80°C freezer at each site until use in the in-parallel mechanistic studies which are being funded separately to the main study. The use of the samples will be limited to the mechanistic studies performed by members of the DEVELOP-UK study group or by designated academic or industrial collaborators. Movement of samples between study centres and to collaborators will be tracked and covered by a comprehensive material transfer agreement.

Each sample will be given a unique identifying code comprising the following:
Centre/ EVLP number/ Type of Sample and number/ Date (DDMMYY)
For example NCL/17/PERF3/030912 represents the code for perfusate sample 3 collected during EVLP run 17 performed in Newcastle on 3rd September 2012.

Centre Codes	**Sample Codes**
NCL = Newcastle	BAL = Bronchoalveolar Lavage
HAR = Harefield	PERF= Perfusate
PAP = Papworth	BIO = Lung Biopsy
BMH = Birmingham	
MAN = Manchester	

Bronchoalveolar Lavage (BAL)
As part of the study protocol, under flexible bronchoscopic guidance a standardised BAL using 120 mls of sterile normal saline (0.9% NaCl solution) will be performed from either the left or right lower lobe of the donor lung on two occasions (BAL1 and BAL2). BAL2 will be performed from the same lobe as BAL1 but should be performed in a different segment of that lobe. The timing of each BAL is detailed below:

BAL 1: At the beginning of the EVLP process after perfusion has commenced and the lung temperature as reached at least 30^{o}C but before ventilation of the lung is initiated.
BAL 2: At the end of EVLP process once the final assessment is complete but before ventilation is discontinued.

For each BAL performed, investigators will record data on the duration of perfusion before the sample is taken, the lobe and segment the BAL is performed in and the volume of saline administered and the volume retrieved. The BAL samples will be processed in an identical way as described below:

A minimum of 2mls to a maximum of 5mls of the total BAL sample will be placed into a sterile container and sent for gram stain and formal microbiological assessment. This will be sent to the microbiology laboratory in each centre for a standard culture and sensitivity assessment. The remaining BAL fluid will be kept on ice until processed which should be performed as soon as possible but certainly within 6 hrs of collection. The BAL will be filtered through gauze to remove excess mucus and then centrifuged to separate the cellular component from the acellular supernatant. The cell pellet will be resuspended in a known volume of phosphate buffered saline and using a haemocytometer the total cell number in the BAL will be calculated. Cytospin slides will then be produced and a differential cell count performed to determine the percentage of neutrophils, macrophages, lymphocytes and epithelial cells present in the BAL. The acellular supernatant will be divided into 1ml alloquots in storage tubes and a maximum of 12 alloquots will be collected from each BAL sample. The storage tubes will then be frozen initially at -20^{o}C and then transferred to a -80^{o}C for longer term storage and subsequent laboratory analysis.

The laboratory investigations will include but are not limited to measurement of a panel of inflammatory and anti-inflammatory cytokines in the BAL fluid using ELISA or other quantitative assays. Other markers of tissue injury, oxidative stress or infection will also be measured.

Perfusate Sampling
Samples of perfusate solution will be collected longitudinally during the EVLP process. 5mls will be collected from the perfusate sampling port at the following times.

Perfusate 0: Taken from the primed EVLP circuit before the donor lung perfusion is started
Perfusate 1: Taken 15 minutes after perfusion is started
Perfusate 2: Taken 30 minutes after perfusion is started
Perfusate 3 to a maximum of Perfusate 8: Taken every 30 minutes during perfusion
Perfusate X: Taken at the end of the perfusion immediately before the perfusion is stopped

The perfusate samples will be centrifuged to remove cellular debris and alloquoted equally into 5x1ml tubes before being frozen initially at -20^{o}C and then transferred to a -80^{o}C for longer term storage and subsequent laboratory analysis. The laboratory investigations will include but are not limited to measurement of a panel of inflammatory and anti-inflammatory cytokines in the perfusate fluid using ELISA or other quantitative assays. Other markers of tissue injury, oxidative stress or infection will also be measured.

Exhaled Gas Collection
To provide samples for in-parallel mechanistic studies, investigators at Harefield Hospital will collect exhaled breath condensate during EVLP. These samples will be taken at the same time as BAL samples for analysis of exhaled nitric oxide (NO), carbon monoxide (CO) and ethylene as markers of lung inflammation. Exhaled breath condensate will be collected with the RTube device (Respiratory Research Inc., Charlottesville, VA), which will be positioned in the expiratory limb of the ventilator circuit. EBC will be collected for 20 min to producing approximately 1mL EBC. pH measurement will be performed after de-aeration with helium gas for 10 min and measured in a gas analyzer. Exhaled NO and CO will be measured by the Logan exhaled breath analyser (Logan Research Inc, Rochester, Kent). Exhaled breath ethylene will be measured by the LPD 300 series ethylene detector by Sensor Sense, (Nijmegen, Netherlands).

Donor Lung Biopsy
Small biopsies of lung tissue will be taken using a Covidien Duet (absorbable buttressed) endo-GIA stapler from either the right middle lobe or lingular at two time points:

Biopsy 1: Taken prior to commencement of the EVLP process at the recipient hospital
Biopsy 2: Taken at the end of the EVLP process once perfusion has stopped

Biopsies will be placed on sterile gauze dampened with 0.9% Saline in a sample pot and the pot stored on ice until processing. From each of these biopsies, a small amount of tissue will be fixed in glutaraldehyde for electron microscopy studies and a small amount snap frozen in liquid nitrogen for subsequent mechanistic studies. The remaining tissue will be fixed in formalin, paraffin embedded and sections cut for Haematoxylin and Eosin staining for routine histological evaluation. Tissue blocks will be available for subsequent immunolocalisation studies using immunohistochemistry.

10.2 Control Intervention
The control intervention is standard lung transplantation.

10.3 Interventions common to experimental and control groups
Donor Pathway
Any potential offer of donor lungs will be communicated to the transplant centres by standard procedures via the SNODs. Each of the 5 centres is then responsible for making an initial assessment of the suitability of the donor lungs for transplant and for determining if they have an

appropriately matched potential recipient on their waiting list. If a centre does not have a suitably matched recipient then the donor lungs will be offered to another centre in a controlled rotational manner run as part of the standard donor organ placement protocol by NHSBT. The donor lung indices will be compared against the donor lung selection criteria for the study and if suitable for potential transplantation then the NHSBT zonal organ retrieval team will be dispatched to the donor hospital to further assess the donor lungs. After careful assessment, a decision will be made using the donor lung criteria (detailed below) as to whether the lungs can be used immediately for standard transplantation, should undergo EVLP assessment and reconditioning or are contraindicated for transplantation. If appropriate for transplant, the donor lungs will then be transported back to the transplant centres according to normal practice.

Donor Lung Procurement for all lungs in the DEVELOP-UK study: The standard lung procurement procedure will be followed for donor lungs to be used for EVLP in the study. In brief, the organs are ante-gradely flushed with supplemented (3.6% THAM 3.3 mls, 0.6 ml CaCl +/- 2.5 mls Prostacyclin / litre) Perfadex®, initially at room temperature, the rest at 4^{o}C. A minimum volume of 60ml/Kg will be given. After the antegrade dose, 200ml will be given down each pulmonary vein as a final retrograde flush. An adequate portion of main pulmonary artery (PA), left atrial cuff and particularly at least 4cm of trachea will be taken by the retrieval surgeon.

10.4 Concomitant interventions

Concomitant Medications: All standard prescribed medications taken by patients on the waiting list for lung transplantation are permitted in the study.
Some medications may be stopped at the time of transplant or in the peri-operative period. These changes will be in line with standard clinical processes and will occur equally to lung transplant recipients in both arms of the study.

Peri and post transplant immunosuppression including any induction therapy and maintenance immunosuppression may vary slightly between centres but will continue to be usual practice during the study. In any of the centres, patients in both the EVLP and standard arms of the study will get the same routine immunosuppressive regimes. The immunosuppressive regimes may however be changed, intensified or reduced in line with standard transplant clinical management of the individual patient and their circumstances.

It is possible that patients awaiting lung transplantation might be enrolled in a CTIMP for their underlying disease. Such medications are stopped at the time of transplant and participation in the CTIMP is censored as an event and therefore their participation in DEVELOP-UK will not be affected.

Patients enrolled in DEVELOP-UK who undergo lung transplant in either the standard or EVLP arm should not be enrolled in any other interventional study in their first 12 months post-transplant that might have an effect on 12 month survival. If there is any question of this, then the local PI must discuss this with the study Chief Investigator who would liaise with the Chief Investigator of the other study and report back to the trial steering committee. Observational non-interventional studies should be allowable but again the local PI must check with the Chief Investigator to make sure there is no interference between the studies. Patients are free to be entered in interventional studies started after their first 12 months post lung transplantation.

Assessments and Data Collection

All study specific follow-up data will be collected during the time of the clinical admission to hospital for the lung transplantation procedure and subsequently at study visits that will be co-ordinated to coincide with routine post-lung transplantation clinic visits. The study research nurse will ensure that routine clinic visits map to the study visit requirements by liaison with study participants and the transplant outpatient facilities in each centre.

The scheduled outpatient study visits will be at 1 month, 3 months, 6 months and 12 months post transplant. A window of +/- 10 days around each timetabled study visit is allowable. If a participant is unable to attend a study visit within the allowable window due to circumstances beyond their control, such as being an in-patient at an external hospital which is not the study centre, then every effort will be made to acquire the same study specific information needed at that visit remotely from the external hospital. No overnight admissions are required for the collection of study specific data. The duration of study participation will commence from the time study consent is taken from a patient on the active waiting list for lung transplant and will finish at the end of the first year after lung transplantation or at the time of patient death either on the waiting list prior to lung transplantation or within the first year after lung transplantation.

The table below details the schedule of study activities and study visits including the data collection requirements at each time point.

Study Events and Data Collection	**Time on waiting list**	**Day of Transplant**	**Post-op ITU stay**	**Post-op inpatient Stay**	**1 month VISIT 1**	**3 months VISIT 2**	**6 months VISIT 3**	**12 months VISIT 4**
Informed Consent or EOI Form	X							
Consent to continue [1]		X						
Donor data		X						
Recipient data	X	X						
EVLP data (if applicable)		X						
ITU data / PGD scores		X	X					
Chest x-ray data		X	X	X	X	X	X	X
Blood profile data			X	X	X	X	X	X
Length of stay data			X	X				
Airway healing data			X	X	X	X	X	
Lung Function data				X	X	X	X	X
Rejection episodes data			X	X	X	X	X	X
Infection episodes data				X	X	X	X	X
Hospital admissions data					X	X	X	X
Patient Perceptions (qualitative interviews)	X						X	
Quality of Life (SF36)	X					X		X
Survival / cause of death	X					X		X
Adverse Events		X	X	X	X	X	X	X

[1] If Informed Consent Form was signed on the day of transplant consent to continue is not required.

The quality of life questionnaires (SF-36) will be self-completed by each study participant (or in conjunction with their nominated proxy).

The assessment of patient perceptions by qualitative interviews will be interviewer-administered by a trained member of the research team. When possible these interviews will be performed face to face at study visits after transplantation. Those interviewed prior to transplant will however be interviewed in their own home or via a telephone interview depending on geographic location. This is because of their precarious health status while awaiting lung transplantation.

No central laboratory analysis is required in the DEVELOP-UK study.

All clinical tests required to determine the success of EVLP assessment and reconditioning of donor lungs including Arterial Blood Gas Analysis, Glucose and Lactate measurement and Microbiological cultures will be performed in each study centre.

Standard blood profiles during follow-up will be performed as part of the recipients routine clinic care and therefore these will be performed in each participating centres certified NHS laboratories and results obtained from hospital data systems.

10.5 Data Handling & Record Keeping

Data will be collected by direct clinical observation, clinical interpretation and from source patient records or NHS documentation by the study clinical research fellow and the study research nurse and then the required data fields will be completed on the eCRF by the research nurse or a designated data manager in each centre under the supervision of the local PI. Data will be held on a validated data management/ data collection system, Symphony, which is GCP and FDA 21 CFR Part 11 compatible. Some of the donor data required for the study will be captured electronically by linking to the core data dataset collected by NHS Blood and Transplant centrally.

Data will be handled, computerised and stored in accordance with the Data Protection Act 1998. No participant identifiable data will leave the study site. Only initials and a unique participant information number will be used on eCRFs and samples leaving the study site. Caldicott Guardian approval will be sought at each site for access to and use of patient identifiable data.

The quality and retention of study data will be the responsibility of Professor Andrew Fisher as the Chief Investigator. All study data will be stored and retained in accordance with the Data Protection Act (1998), the latest Directive on GCP (2005/28/EC) and local policy.

11. Statistical Considerations

11.1 Proposed sample size

It is proposed that the study will accumulate patients over a three year period, with the possibility that a one year extension will be requested following an interim analysis scheduled to take place after 24 months. In the standard arm, the current best available estimate for survival to 30 days is 94.2%, to 90 days is 91.2% and to 1 year is 78.7%. These data are determined from the Royal College of Surgeons UK national audit of lung transplant outcomes. Our aim is to demonstrate that using reconditioned EVLP lungs does not increase the hazard rate of death during the first year by more than a factor of two. A doubling of the hazard rate would imply that survival rates on EVLP would be 88.7% for 30 days, 83.2% for 90 days and 61.9% for one year. Such a difference was not felt to be clinically significant, and to represent an advantage over waiting longer for a transplant.

As described above it is not clinically, logistically or ethically possible to randomise recipients to the standard or EVLP arms of the study. EVLP is being evaluated for its ability to safely increase lung transplant activity and therefore recruitment into the EVLP arm will represent an increase in activity in each centre. Pre-existing levels of transplant activity will continue and will constitute the standard (or control) arm of the study. As a result approximately three times as many patients will be recruited in the standard arm than in the EVLP arm. Over three years, it is anticipated that 100 EVLP lungs will be transplanted, and 300 or more normal lung transplants will take place. If both treatment arms match the standard 78.7% rate of survival over 12 month, then approximately 85 deaths will occur within one year of transplantation. Using a fixed sample design, this is sufficient to ensure an 80% power of claiming a significant finding of non-inferiority (at a one-sided 5% level) if both treatment groups actually have the same survival pattern (29). The study is powered to detect a difference of 2 meaning that Non-inferiority is assumed if the hazard rate is not doubled by the use of EVLP.

We are proposing to use an adaptive design for our study to allow for the possibility of stopping the trial early should non-inferiority in our primary outcome be determined at an interim analysis and to re-evaluate the sample size requirements on the basis of potentially improved standard of care. It is felt that a total of 3 analyses (2 interim and one final) will achieve a suitable balance between allowing for early-stopping and ensuring that sufficient data are collected on secondary outcome variables. These interim analyses will take place once a pre-specified number of patients have been recruited to each arm. We have elected to use the O'Brien-Fleming critical values for the analyses during our study; these are chosen so that the overall study achieves a significance level of 0.05 once allowance has been made for the interim analyses. The choice of O'Brien-Fleming over the alternative methods (such as the Pocock boundaries which allocate equal critical values for all analyses) has the added benefit that the final analysis is closely comparable to the analysis of a standard design. In practice, we would effectively carry out the first interim analysis at a significance level of 0.005, the second at 0.014 and the final at 0.045; the overall procedure then has a significance level of 0.05.

To obtain sample sizes for this adaptive design we take the standard sample size and multiply it by the appropriate inflation factor (which depends on the choices of critical values, number of analyses, significance level and power). For our choices the inflation factor is 1.0128 resulting in a sample size of 304 in the standard arm and 102 in the EVLP arm. We raise these to 306 in the standard arm while keeping 102 in the EVLP arm in order that the sample size in both arms are divisible by 3 to allow for equally spaced interim analyses. This results in a required minimum total sample size of 408 with interim analyses after 12 month survival data is available from 102 and 204 patients in the standard arm (34 and 68 in the EVLP arm).

A further objective of the 2nd interim analysis, besides an early claim of non-inferiority, is to re-evaluate the sample size requirements for this trial. Although the above calculations are based on the best currently available estimates, continuing improvement in the standard of care could result

in further improved survival in the control group. If this were the case, then fewer deaths would be observed over the three years of the study, and the desired power of 80% would be compromised. Thus, potential for failing to claim non-inferiority despite EVLP being equivalent or even better than the standard would be increased.

Should non-inferiority be established for the primary outcome measure at the interim analysis a decision will be taken by the Trial Steering Committee with input from the Data Monitoring Committee and in consultation with the HTA Board on whether to continue recruitment in order to collect sufficient important secondary outcome data or to cease recruitment and perform final data analysis once data collection is complete on the patients enrolled in the study. Similarly, if the sample size re-evaluation suggests that the survival on standard has improved to an extent that it compromises the power specification, a sample size increase up to at most 102 patients in the control arm and 34 in the EVLP arm, which corresponds to an extension by at most 12 month, will be discussed within the Trial Steering Committee and with the HTA Board.

11.2 Statistical analysis

Statistical analysis will be conducted in a number of parts, firstly a comparison of outcomes between recipients of standard and EVLP transplants to establish non-inferiority and secondly to model the effect of EVLP transplants on the overall survival of patients accepted for lung transplantation in the UK to assess the impact on the service. Further, additional analyses will also be undertaken to identify clinical predictors from the donor of successful EVLP reconditioning.

Comparison of outcomes between recipients of standard and EVLP transplants

The analysis of outcomes of standard and EVLP transplants is a comparison of contemporaneous cohorts and will follow the principles of the STROBE guidelines where possible. All consented patients who undergo lung transplantation with or without EVLP grafts will be included. The proposed analysis strategy, as with the sample size determination, for the comparison of outcomes between recipients of standard and EVLP transplants will follow approaches outlined in Jennison and Turnbull (30), but will also consider techniques outlined in other publications.

- Our primary outcome of survival during the first 12 months will be analysed for non-inferiority of EVLP using standard methods for survival data at each interim analysis time point.
- Covariates will be adjusted for using proportional hazards models and these analysis methods will be adjusted appropriately should relative recruitment rates differ from those expected, using approaches described in Jennison and Turnbull (30).
- The method of selection of covariates for use in the model will follow standard techniques of model comparison (e.g. stepwise procedures) considering both the significance of the terms in addition to the overall fit.
- It is intended that analysis will take place when both arms have reached at least the target recruitment for the specific analysis time point.
- It is this analysis of the primary outcome which will determine whether or not the study proceeds past each interim analysis and so will be used to demonstrate non-inferiority, or otherwise, of EVLP compared to standard treatment.

As the study is not randomised it will be necessary to include a range of covariates in the analysis to reduce bias from systematic selection and increase precision in the estimate of the group difference. There are a number of donor, recipient and procedure related variables that mean that lung transplants are a heterogeneous group, so that it will be important to stratify analyses by

- Recipient diagnosis (cystic fibrosis, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, other)
- Other recipient characteristics (age, gender, body mass index, FEV_1, diabetic status)
- Donor characteristics (age, sex, ischaemic time, donor type DBD or DCD)
- Transplant procedural variables (i.e. single, bilateral or heart-lung transplant, and use of cardiopulmonary bypass)

These potential covariates have been identified from the ISHLT Registry as those shown to potentially influence outcomes. Not all these covariates will be included in the final model, but their potential inclusion will be explored using the method of covariate selection described for the primary outcome analysis above.

Assessment of secondary outcome measures
The secondary outcomes to be considered are:
Survival at 90 days post transplant
Primary Graft Dysfunction (PGD) score at 24, 48 and 72hrs post transplant
Duration of invasive ventilation in hrs and ITU stay in days
Duration of hospital stay before first discharge in days
Presence of post-operative infection, rejection or anastomotic complications
Lung function measurements (FEV_1 and FVC % predicted)
Presence of specific abnormalities on chest x-rays
SF-36 quality of life measure

The measures will be collected at a number of specific time points and will be similarly analysed using appropriate techniques such as those defined above in addition to logistic regression (including multinomial as appropriate) and Analysis of Covariance (ANCOVA) methods once the final analysis of the primary outcome has been undertaken. The use of non-parametric tests will be considered should normality assumptions be violated.

From clinical experience of this patient group, it is not anticipated that there will be any drop-out or loss to follow-up of patients with respect to the primary outcome measure. Loss to follow-up or missing data on the secondary outcome measures will be assessed and although very unlikely, if a sufficient quantity of data is found to be missing (greater than approximately 10%) the complete case analysis will be compared with one using imputation methods. In this approach those with missing data will be compared with those with complete data on key covariates, using appropriate statistical tests, to assess for potential biases.

Modelling the effect of EVLP on the overall survival of patients awaiting transplantation
To capture the effects that an increased availability of donor organs might have on the quality or length of life of transplant patients, we propose a secondary analysis that considers the effects of a reduction in the time a person waits for a donor lung. A model will be developed which describes the key events pre and post transplant (31). The model will begin when a patient joins the waiting list, include the standard or EVLP transplant and end with post transplant survival. As well as post transplant survival, death whilst awaiting transplant will also be included in the model. This will allow any bias introduced because of the competing risk of death whist awaiting transplant to be removed from the model. To allow a comparison to be made with outcomes without an increased availability of donor organs historical data on waiting time to lung transplant and waiting list deaths will be available from NHSBT for comparison.

Identifying Clinical Predictors of successful EVLP reconditioning
A logistic regression approach will be used to examine the association between successful reconditioning and a number of potential predictors based on donor characteristics and indices measured during EVLP and subsequent successful EVLP assessment and reconditioning. Successful EVLP will be defined as a donor lung that satisfies all the criteria for use in clinical lung transplantation as stated in this study protocol.

Similar approaches will be undertaken examining EVLP donor lungs used in transplantation and the association between early clinical outcome measures in recipients and physiological indices measured during EVLP. This will require using logistic or linear regression as appropriate for the outcome under investigation (i.e. linear regression with appropriate transformations if necessary, for continuous dependent variables and logistic regression for binary dependent variables).

In terms of the data to be included, this will follow a similar protocol to that outlined above in comparing outcomes between recipients of standard and EVLP transplants. The following measures will be considered:

- Donor (age, sex, cause of death, smoking history, ischaemic time, donor type DBD or DCD)
- EVLP Physiology (Blood gases, lung compliance and resistance, airway pressure perfusion time etc.)
- Recipient outcomes as listed above in the primary and secondary outcomes

The method of selection of covariates for use in the model will, similarly, follow standard techniques of regression modelling considering both the significance of terms added to the model, in addition to the overall fit. Regression diagnostics will be done for all models, including assessments of residuals and checks that all assumptions have been adhered to.

12. Economic Analysis

The main part of the economic evaluation in this study will consist of a cost-effectiveness study and a cost-utility analysis. Depending on study results, the number of transplant survivors at 12 months will be used as the denominator in the incremental cost-effectiveness ratio. To enable this we will calculate the incremental (total) NHS cost of using EVLP to generate 102 additional sets of donor lungs to a point where they accepted for use in lung transplantation. This will include all staff, materials, retrieval team travel costs to potential organ donor sites, and equipment costs as incurred at the study sites. As this is likely to be a key issue this figure will form an important part of any sensitivity analysis undertaken. The 90 day and 12 month mean cost of caring for lung transplant recipients of EVLP assessed and reconditioned donor lungs and standard donor lungs will also be assessed to give a mean total cost for the type of lung transplant undertaken. This will show if there are any additional post-transplant costs associated with use of EVLP reconditioned lungs with comparator data being taken from a prospective assessment of recipients of standard donor lungs. At the same post-transplant time points (90 days and 12 months), QOL will be determined using the SF-36 in all recipients. This will allow us to use the SF-6D (32) to assess health state utility scores in recipients of EVLP lungs compared with the utility values from recipients of standard donor lungs. Extensive deterministic (e.g. to explore the impact of different mix of staff, materials etc.) and probabilistic sensitivity analysis (to explore statistical imprecision surrounding estimates) will then be undertaken (33).

13. Interview sub-study analysis

The aim of this embedded 24 month interview sub-study is to identify, describe and understand patients' pre and postoperative perceptions of EVLP, and to explore how these are mediated by individual, social, physical and clinical factors. We do not know what patients think about EVLP and research related to people's experiences of receiving donor organs is also limited, therefore this study will refer to the broader sociological literature pertaining to people's experiences of health, illness and health care (34) to inform data collection and analysis.

Focused interviews will be conducted with individuals, these are particularly useful when researching a new area about which relatively little is known (35). They are flexible enough to allow interviewer and interviewee to explore issues which are pertinent to the individual person and which were not anticipated in advance, thus enabling a fuller understanding of the subject under discussion. The interviews will cover the following broad areas: Pre-operatively a) patients' accounts of their own health and experience of living with their condition b) patients' experiences of waiting for a lung transplantation c) their understandings of EVLP and the perceived acceptability of this procedure in comparison with other donor lungs and e) their hopes and expectations for EVLP. Post-operatively a) patients' accounts of their preoperative health and experiences b) accounts of waiting for a transplant c) views and experiences of receiving and living with an EVLP transplant.

Location: This study will be conducted in two sites namely Freeman Hospital, Newcastle and Harefield Hospital; these have been chosen as they will be recruiting the largest number of patients to the study and performing more EVLP transplants, and because both sites provide access to diverse surrounding populations. Participants at both hospitals are likely to be geographically dispersed and will be given the opportunity to be interviewed face to face either in their own home or in a suitable room in the hospital they are attending to coincide with existing appointments or if they prefer they may choose to be interviewed by telephone. To this end, in addition to the experienced research associate, the two research nurses at both of these sites will need to have the requisite skills to conduct qualitative interviews.

Sampling: The sample will comprise between 20-30 (10-15 in each site) patients waiting for a lung transplantation and 20-30 patients 3-6 months post-operative. All respondents will be over 18 years of age. We are aware that asking people waiting for a lung transplantation to speak at length in an interview may be challenging for them, and therefore we will offer them the option to invite their nominated carer to participate in the interview with them. Maximum variation purposive sampling and theoretical sampling (36) will be used to ensure the views of people of different ages and backgrounds, and with different conditions are represented in the data set. As data collection and analysis progresses to ensure the validity and robustness of our analysis we will deliberately seek out individuals who may have different views and experiences.

Recruitment: On consenting to be part of the trial all patients recruited at Freeman Hospital or Harefield Hospital will be informed they may be invited to take part in an interview about their views of EVLP. It will be made clear that this is an optional part of the study. Pre-operative patients At month 3 the interview sub-study will commence and patients waiting for a transplant operation at both sites will be sent a letter and sub-study information sheet from the local PI inviting them (and a nominated carer) to participate in an interview. Patients will only be written to once. Participants will opt-into the study by returning a consent form. Once the consent to contact form has been received by the team a locally based researcher will contact the patient to arrange an interview either at a place of their choice or over the telephone. During recruitment the team will constantly check the socioeconomic, age and clinical profile of participants and actively target under-represented groups. Post-operative patients Selected patients who have received a lung transplant and are enrolled in the study will be invited between 3 and 6 months post operatively to take part in an interview, after consultation with the local clinical team. Again, the same process will be followed and patients will have the opportunity to 'opt-in' to this part of the study.

Data Preparation and Analysis: All interviews will be digitally recorded and transcribed verbatim. In line with Data Protection Legislation and Research Governance all information pertaining to individuals will be anonymised. The qualitative analysis will adopt a constructivist grounded theory approach (37). Following a long tradition in qualitative research (38) data collection and analysis will occur concurrently to allow for issues or themes identified in earlier interviews to be explored in more depth in subsequent interviews. Open, then focused coding, will be undertaken and emergent codes from the analysis of this stage will be presented to the wider research team. The validity of data interpretation will be ensured by independent coding and cross-checking by at least two members of the research team. A suitable software package (e.g. NVivo) will be used to facilitate data analysis management.

Analytic framework: In order to deliver the aim of this sub-study, an analytical framework will be applied to the data to ascertain how patients' attitudes, views and experiences of EVLP transplantation may be mediated by different social, psychological and clinical factors. Specific attention will be given to how the following factors shape patient views and experiences of EVLP:

1. Self-identity – the effect of self-perception and self-esteem
2. Health experience – the effect of symptoms, functionality, and perceived quality of life
3. Life-world – the effect of personal relationships (e.g. family, friends), socioeconomic circumstances, and interactions within the patient's life
4. Clinical world – the effect of the clinical setting (e.g. Practitioner advice; knowledge of treatment; previous treatments, availability of treatment)

Outcome*:* It is imperative if new heath care technologies are to be enacted successfully that to achieve real benefits for patients the views of those receiving them are taken into accounts. The outcome of this sub-study will identify and specify how a range of social, psychological, and clinical factors affect people's attitudes and experiences of EVLP. These results will help inform and improve future practice development.

14. Compliance and Withdrawal

14.1 Compliance with EVLP protocol

The protocol determining the selection of donor lungs to undergo EVLP and indices which determine whether the lungs are suitable for transplant after EVLP have been clearly described in the study protocol. To ensure compliance with the protocol, data will be collected about the donor assessment and EVLP procedure. This will allow confirmation that the donor lung was appropriately allocated to undergo EVLP and that the decision on its suitability was correctly determined. If there are any instances identified whether the protocol was not followed, this will be recorded as a protocol deviation and the monitors will ask the local PI to explain and document why the protocol deviation occurred.

14.2 Compliance of participants

Transplanted lungs, whether 'standard' or EVLP reconditioned, always remain vulnerable to the possibility of rejection and one of the main risk factors is low immunosuppression levels. For this reason patients are heavily counselled prior to being accepted onto the transplant list about the necessity of absolute concordance with their treatment and in attending all arranged post-transplant follow-up appointments. As a result, during the multi-disciplinary pre-transplant assessment a considerable amount of time is spent explaining this aspect of care to the patients. If despite these attempts there remains evidence of non-compliance with treatment these individuals would not usually be offered the option of transplantation.

The inherent complexity of lung transplantation requires that the patients are followed-up in centres with experience in the short- and long-term management of these patients. All patients are given the opportunity of life-long follow up at their respective transplant centre. At the time of assessment and listing, the nature of this process is fully explained. This level of detailed explanation and the understanding that develops with the patient ensures that exceptionally few are lost to follow up (less than 1%) other than through death (approximately 20% at 12 months). The possible scenario where this could happen is if a patient withdrew their consent from the study and does not wish any further study related data to be collected. If this situation did arise patients would continue to receive standard post-transplant care; data collected to the point of withdrawal would be retained and analysed (the participant information sheet will make this clear).

14.3 Withdrawal of participants

Participants have the right to withdraw from the study (the trial, interview sub-study or both) at any time for any reason, and without giving a reason. The investigator also has the right to withdraw patients from the study intervention if s/he judges this to be in the patient's best interests. It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible.

If a patient listed for transplant initially consents to DEVELOP-UK prior to the day of transplant but then does not re-consent using the consent to continue on the day of transplant, s/he will be considered to have withdrawn from the study and no follow-up data will be collected.

If a patient listed for transplant signs an Expression of Interest (EOI) Form and then signs a consent form on the day of transplant re-consent using the consent to continue is not required and follow-up data can be collected as normal.

If a patient receives a lung transplant (either EVLP or standard) but subsequently requests to withdraw from follow-up data collection, including completion of questionnaires, data collected up to

the point of withdrawal will be retained (this will be made explicit in the participant information leaflet). Withdrawing participants will be asked if they are willing for continuation of collection of those data items that can be extracted from their routine records and if they would be happy for the reason for the decision to withdraw to be recorded.

15. Data Monitoring, Quality Control and Quality Assurance

15.1 Discontinuation rules

At the planned interim analyses, it will be determined if the study has satisfied its primary endpoint of showing non-inferiority of EVLP in 12 month survival after lung transplantation. If this is achieved, a decision will be made by the Trial Steering Committee in consultation with the sponsor and funder as to whether to continue the study to gain valuable secondary outcome data.

The trial may be prematurely discontinued on the basis of new safety information, or for other reasons given by the Data Monitoring & Ethics Committee and/or Trial Steering Committee, Sponsor, or Ethics Committee concerned.

15.2 Monitoring, quality control and assurance

The trial will be managed through Newcastle University. The Trial Management Group (TMG) will include: the Chief Investigator, Senior Trial Manager, Trial Manager, assistant trial manager and other members of the trial team when applicable.

Newcastle CTU will provide day-to-day support for the sites and provide training through Investigator meetings, site initiation visit and routine monitoring visits.

The Principal Investigators will be responsible for the day-to-day study conduct at each of the five participating sites.

Quality control will be maintained through adherence to Newcastle Biomedicine Clinical Research Platform and study-specific SOPs, this study protocol, the principles of GCP, research governance and clinical trial regulations.

Data Monitoring and Ethics Committee (DMEC)

An independent data monitoring and ethics committee (DMEC) has been appointed. The role of the DMEC will be to monitor the accumulating data from both arms of the trial and to make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue. In its deliberations, the safety, rights and well-being of the trial participants will be paramount. Members of the DMEC will be fully briefed about the potential for bias and will be asked to review the accumulating data for any confounding effects.

Responsibility for calling and organising DMEC meetings lies with the Professor Fisher as Chief Investigator, in association with Professor Flather, the Chair of the DMEC. The project team will provide the DMEC with a comprehensive report, the content of which should be agreed in advance by the Chair of the DMEC. DMEC meetings will be timed so that reports can be feed into the TSC.

DMEC membership: Professor Marcus Flather, R&D Director and Professor of Clinical Trials at Norfolk and Norwich NHS Trust and University of East Anglia Medical School is the independent chair; Dr Paul Aurora, paediatric lung transplant physician from Great Ormond Street (GOS) Hospital as the clinical expert; Professor Sue Todd, from the University of Reading, an experienced independent trial statistician with specific expertise in adaptive trial design. At the first meeting, the DMEC will agree on its charter of operation.

The DMEC may be asked by the TSC, Trial Sponsor or Trial Funder to consider data emerging from other related studies.

Trial Steering Committee (TSC)

A trial steering committee will also be convened. The remit of the TSC will be in line with HTA expectations, as follows:

- The role of the TSC is to provide overall supervision for a trial on behalf of the Trial Sponsor and Trial Funder and to ensure that the trial is conducted to the rigorous standards set out in the Medical Research Council's (MRC) Guidelines for Good Clinical Practice.
- In particular, the TSC should concentrate on progress of the trial, adherence to the protocol, patient safety and the consideration of new information of relevance to the research question.
- The safety and well-being of the trial participants are the most important considerations and should prevail over the interests of science and society.
- The TSC should provide advice, through its chair, to the Chief Investigator(s), the Trial Sponsor, the Trial Funder, the Host Institution and the Contractor on all appropriate aspects of the trial.
- Representatives of the Trial Sponsor and the Trial Funder should be invited to all TSC meetings.
- Responsibility for calling and organising TSC meetings lies with the Chief Investigator. The TSC should meet at least annually, although there may be periods when more frequent meetings are necessary.
- The TSC will provide evidence to support any requests for extensions, indicating that all practicable steps have been taken to achieve targets.

TSC Membership: The independent chair will be Dr Duncan Young, Consultant & Senior Clinical Lecturer in Anaesthetics and Intensive Care. Professor Dirk Van Raemdonck, an active researcher in the field of primary graft dysfunction after lung transplantation will be a Committee member. There will also be an independent statistician Dr Chris Weir, independent health economist Dr Paul McNamee, independent trials methodologist Dr Chris Rogers and two lay members Mr Chris Wiltsher and Ms Lesley Costello along with Professor Fisher (Chief Investigator), Miss Karen Redmond (Surgical Lead and Co-Investigator), Dr Tom Chadwick (study statistician), trial manager Jessica Qian and senior trial manager Dr Jennifer Wilkinson. Observers from the HTA programme and the sponsor will be invited to all TSC meetings.

Study Monitoring

Monitoring of study conduct and data collected will be performed by a combination of central review and site monitoring visits to ensure the study is conducted in accordance with GCP. Study site monitoring will be undertaken by Newcastle CTU staff. The main areas of focus will include consent, serious adverse events and essential documents in study.

Site monitoring will include:

- All original consent forms will be reviewed as part of the study file. The presence of a copy in the patient hospital notes will be confirmed for 100% participants
- All original consent forms will be compared against the study participant identification list
- All reported Serious Adverse Events (SAEs) will be verified against treatment notes/medical records (source data verification)
- The presence of essential documents in the investigator site file and study files will be checked
- Source data verification of primary endpoint data and eligibility data for 10% of participants entered in the study

Central monitoring will include:

- All applications for study authorisations and submissions of progress/safety reports will be reviewed for accuracy and completeness, prior to submission
- All documentation essential for study initiation will be reviewed prior to site authorisation

All monitoring findings will be reported and followed up with the appropriate persons in a timely manner.

The study may be subject to inspection and audit by The Newcastle upon Tyne Hospitals NHS Foundation Trust under their remit as sponsor, and other regulatory bodies to ensure adherence to GCP. The investigator(s)/institutions will permit trial-related monitoring, audits, REC review and regulatory inspection(s), providing direct access to source data/documents.

16. Adverse Event Monitoring and Reporting

RECs require that all SAEs occurring to a trial participant be captured and reported. A system for monitoring, capturing, recording and reporting SAEs is therefore included in the study protocol.

16.1 Definitions

Adverse event (AE): Any untoward medical occurrence in a subject to whom a study intervention or procedure has been administered, including occurrences which are not necessarily caused by or related to that intervention/procedure. An AE, therefore, does not necessarily have a causal relationship with the research procedure/intervention. Medical conditions/diseases present before starting the research procedures are only considered adverse events if they worsen after starting study treatment.

Related AE: An AE that results from administration of any of the research study procedures. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a study procedure qualify as 'related adverse events'. The expression "reasonable causal relationship" means to convey in general that there is evidence or argument to suggest a causal relationship.

Causality:

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below. All adverse events judged as having a reasonable suspected causal relationship to a study procedure (i.e. definitely, probably or possibly related) are considered to be related adverse events. If any doubt about the causality exists, the local investigator (PI) should inform the Chief Investigator. In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the main REC and other bodies will be informed of both points of view.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study procedure). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the study procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

Unexpected Adverse Event: An adverse event that is not listed in the study protocol as an expected occurrence in the circumstances of this trial.

Serious Adverse Event (SAE): an untoward occurrence (whether expected or not) that:

- Results in death
- Is life-threatening, requires hospitalisation, or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
  Or
- Is otherwise considered medically significant by the investigator

The term life-threatening refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

Medical judgement should be exercised in deciding whether an adverse event is serious in other situations. Important adverse events (related or otherwise) that are not immediately life-threatening or do not result in death or hospitalisation, may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definitions above, should also considered serious.

Notes:
SAEs that are also related and unexpected require expedited reporting within strict timelines.

Severity (intensity) of Adverse Events
Severity of all AEs will be graded on a three-point scale of intensity (mild, moderate, severe):
- Mild: Discomfort is noticed, but there is no disruption of normal daily activities.
- Moderate: Discomfort is sufficient to reduce or affect normal daily activities.
- Severe: Discomfort is incapacitating, with inability to work or to perform normal daily activities.

16.2 Protocol Specifications

For purposes of this protocol:
- All adverse events will be recorded prior to hospital discharge at all study visits and categorised as to expectedness, relatedness and severity.
- Any serious adverse events will be recorded throughout the duration of the trial until 12 months post-transplantation
- Serious adverse events exclude any pre-planned hospitalisations (e.g. elective surgery or planned bronchoscopies) not associated with clinical deterioration.
- Serious adverse events exclude routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- Serious adverse events exclude elective or scheduled treatment for pre-existing conditions that did not worsen during the study.

Serious adverse events requiring urgent reporting include:
- Death within 90 days of lung transplantation
- Severe Primary Graft Dysfunction requiring ECMO/Novalung support
- Bronchial anastomotic dehiscence
- Any unexpected SAE felt to be probably or definitely causally related to EVLP

Serious adverse events excluded from urgent reporting:
- Death on the waiting list prior to transplant
- Death greater than 90 days after lung transplantation
- Primary Graft Dysfunction grade 1 to 3 not requiring ECMO/Novalung support
- Severe sepsis associated with consolidation, necrosis or cavitation of lung tissue within 30 days of transplant
- Renal failure necessitating renal replacement therapy
- Gastrointestinal complications
- Central nervous system complications

- Infections requiring an addition or change in anti-microbial therapy
- Bronchial stricture whether or not requiring bronchial stenting
- Acute rejection requiring augmented immunosuppression
- Development of post-transplant lymphoproliferative disease
- Development of obliterative bronchiolitis
- Deterioration of pre-existing medical conditions both pre and post transplant

16.3 Recording & Reporting Serious Adverse Events

Only adverse events that are not part of usual expected recovery events after lung transplantation should be reported. Depending on the nature of the event, the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance or their nominated deputy.

Adverse Event (AEs): All adverse events during study participation will be reported on the study CRF and sent to Newcastle Clinical Trials Unit within four weeks of the event. The individual investigator at each site will be responsible for managing all adverse events according to local practice.

Serious Adverse Event (SAEs): SAEs requiring urgent reporting shall be reported on the DEVELOP-UK SAE form to the Newcastle Clinical Trial's Unit within 24 hours of the PI learning of the occurrence. A secure fax line is available for this purpose (0191 5800434). SAEs excluded from urgent reporting should be reported on the study CRF.

The initial report should contain the following minimum information*:

1. Study identifier (Protocol number)
2. Participant's unique study number
3. Participant's date of birth
4. Event description
5. Start date of event
6. Reason for severity grading (i.e. death, life-threat, hospitalisation, disability/incapacity)
7. Reporters name, signature and date

*In the case of incomplete information at the time of the initial reporting, all appropriate information should be provided as follow-up as soon as it becomes available.

Hospitalisations for elective treatment of a pre-existing condition or hospitalisations as part of routine post-transplant surveillance do **not** need reporting as SAEs. Unrelated hospitalisations will be elicited at the follow up appointment, scheduled subsequent appointments and all emergency appointments.

Serious Adverse events that are related and unexpected should be reported to main REC within 15 days of Chief Investigator becoming aware of event according to the guidelines set out by NRES. (http://www.nres.npsa.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-all-other-research/)

This is the responsibility of the sponsor (or authorised delegates).
Local investigators should also report any SAEs as required by their Research & Development Office.

Contact details for reporting SAEs
Fax: 0191 5800434, attention NCTU DEVELOP-UK Trial Manager

17. Ethics & Regulatory Issues

The conduct of this study will be in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions. All members of the research team, and the investigators and supporting staff at each of the participating sites will receive training in those aspects of Good Clinical Practice appropriate to their role in the trial, in particular the processes for obtaining informed consent including the requirements of the Mental Capacity Act, and will be expected to operate to principles of GCP.

A favourable ethical opinion from an appropriate REC and R&D approval will be sought prior to commencement of the study. Local approvals will be sought before recruitment may commence at each site. The Newcastle Clinical Trials Unit, in its capacity as study coordination centre, will require a written copy of local approval documentation before initiating each centre and accepting participants into the study.

Information sheets will be provided to all eligible subjects and written informed consent obtained prior to any study procedures. Patients on the transplant waiting list who live a significant distance from the transplant centre will be given the opportunity to sign an expression of interest (EOI) which allows them to subsequently be consented when attending the transplant centre which may be on the day of transplant. Signing of the EOI Form permits completion of the first SF-36 questionnaire.

We will obtain informed and voluntary consent via an iterative process, providing adequate time (i.e. a period of not less than 24 hours) for consideration and discussion of the clinical and research aspects of the study. Initial consent will be taken at the time a patient is listed for lung transplant. For those patients already on the transplant list at the time of study initiation, consent will be sought when the study opens at their transplant centre. Re-consent on the day of transplant will be sought only from patients consenting to the study prior to the day of lung transplant.

Additional informed consent, using a separate participant information sheet and consent form, will be sought from the subset of patients approached to take part in the interviews for the qualitative sub-study; lack of consent to take part in this element of the study will not preclude participation in the study.

If a potential participant is unable to provide written consent because of visual or motor impairments, or literacy problems, oral informed consent will be taken in the presence of an independent witness (who will initial, sign and date the consent form on the participant's behalf). We do not anticipate that any potential study participants will lack capacity to consent on recruitment to the study, it is however possible that they could lose capacity over the follow-up period. For example, if as a result of transplant surgery any participant were to lose capacity temporarily or permanently such as by requiring prolonged ventilation on the intensive care unit or by suffering a stroke, we will aim to continue to collect outcome measures in relation to such patients, working with personal or nominated consultees and in line with the requirements of the Mental Capacity Act. As much of the data is observational, its collection will not impact on the standard care than any participant that has lost capacity would receive.

Patients waiting for transplantation are desperately sick, very vulnerable and grasping at any lifeline. Securing genuinely informed consent is therefore an important consideration. The initial consent process will take place well ahead of the time of transplant and the stressful environment that this generates. During the consent process, care will be taken not to unjustifiably inflate hope of a shorter waiting time for transplantation as a result of EVLP being available. A clear definition of what constitutes an unusable donor lung in the study will be explained as definitions of acceptability of lungs for standard transplantation and for transplantation after EVLP will be standardised across all centres. Patients will be offered firm reassurance that if donor lungs do not improve sufficiently after EVLP reconditioning to satisfy acceptability criteria they will not be used. Any potential recipient who

decides not to participate in the DEVELOP-UK study will have equal access to donor lungs for standard transplant.

18. Confidentiality

Personal data will be regarded as strictly confidential. To preserve anonymity, any data leaving the site will identify participants by their initials and a unique study identification code only. The study will comply with the Data Protection Act, 1998. All study records and Investigator Site Files will be kept at site in a locked filing cabinet with restricted access.

All laboratory samples will be labelled with a unique study identification number as described in the previous section *Sample Collection, Processing and Storage* (linked in anonymised form).

19. Insurance and Finance

The participating sites are all NHS Trust and as such have liability for clinical negligence that harms individuals toward whom they have a duty of care. NHS Indemnity covers NHS staff and medical academic staff with honorary contracts conducting the trial for potential liability in respect of negligent harm arising from the conduct of the study. The Newcastle upon Tyne Hospitals NHS Foundation Trust is Sponsor and through the Sponsor, NHS indemnity is provided in respect of potential liability and negligent harm arising from study management. Indemnity in respect of potential liability arising from negligent harm related to study design is provided by NHS schemes for those protocol authors who have their substantive contracts of employment with the NHS and by Newcastle University Insurance schemes for those protocol authors who have their substantive contract of employment with the Newcastle University. This is a non-commercial study and there are no arrangements for non-negligent compensation.

The NIHR Health Technology Assessment programme is funding the study.

Vivoline are providing EVLP machines on loan to each site for the duration of the treatment phase of the study and have also agreed to provide the consumables kits for each EVLP assessment at a matching cost to what has been made available to the study by NCG through excess treatment cost (£3700 per EVLP assessment). Vivoline as a commercial entity have had no influence on the study design and will have no ongoing involvement within study governance. They have however agreed to provide a rolling programme of on-site training on equipment in each centre, to provide a technical telephone helpline and on-site maintenance or replacement in the event of any equipment failures. These provide further ways in which the provision of EVLP can be standardised and maintained continuously during study recruitment.

20. Study Report / Publications

All study data will be the property of the Chief Investigator, Co-Investigators and Principal Investigators. Publication of any study results will be the responsibility of the Chief Investigator and will be published under authorship arrangements agreed with the Co-Investigators and all Principal Investigators.

Each proposed publication will be considered by the Chief Investigator, Co-Investigators and Principal Investigators as part of a publication plan. The Chief Investigator can at their discretion appoint one or more of the other study investigators to take a lead in preparation of a particular abstract or manuscript depending on the proposed content and the specialist expertise of the investigators.

It is planned to publish study results in peer reviewed scientific journals and to present study data at national and international meetings. Results of the study will also be reported to the Sponsor and Funder, and will be made available on the latter's web site. Individual study participants must not be identified or be identifiable in any study report or publication.

All manuscripts, abstracts or other modes of presentation must be reviewed by the Trial Steering Committee at least 60 days and by the Funder at least 28 days prior to planned submission. Submission can only occur once approved by the TSC and the Funder.

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22. Appendices

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Appendix 1 Study Consent Form (Example)

To be printed on the local trust headed paper

Centre Number:

Study Number:

Participant Identification Number:

DEVELOP-UK

A Study of Donor Ex-vivo Lung Perfusion in United Kingdom Lung Transplantation

Participant Consent Form

Please initial box

1.	I confirm that I have read and understand the Participant Information Sheet dated 01 November (version 1.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2.	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
3.	I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from Sponsor (The Newcastle upon Tyne Hospitals NHS Foundation Trust) or its representatives, or from regulatory or ethical authorities where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
4.	I understand that small samples of lung tissue will be collected from donor lungs during ex-vivo lung perfusion (EVLP). I accept that these samples will be used by the research team and by academic or industry partners some of whom may be outside the United Kingdom.	☐
5.	If as a result of transplant surgery I were to lose capacity temporarily or permanently I agree that the collection of observational data from my medical records can continue.	☐

6. I understand that if, for any reason, I withdrew from the study, the researchers will still be able to use any data collected during the time I have been taking part in the study. ☐

7. I agree to my GP being informed of my participation in the study. ☐

8. I agree to take part in the above study. ☐

Name of Participant	Date	Signature

Name of person taking consent	Date	Signature

If a participant is able to give informed consent but unable to sign this consent form, consent should be confirmed orally in the presence of a witness.

Name of Participant

Name of witness	Date	Signature

When completed: one copy to participant; one copy for hospital record; original copy to Site Investigator File.

Appendix 1 Interview Study Consent Form (Example)

To be printed on the local trust headed paper

Centre Number:

Study Number:

Participant Identification Number:

DEVELOP-UK

A Study of Donor Ex-vivo Lung Perfusion
in United Kingdom Lung Transplantation

Interview Study

Participant Consent Form

Please initial box

1. I confirm that I have read and understand the Participant Information Sheet dated 01 November 2011 (version 1.0) for the above Interview study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I received enough information about the study and I understand what the study involves. ☐

3. I understand that the Interview study is purely optional and I can withdraw from this study at any time and do not have to give a reason for doing so. I understand I will not be contacted again with regards to the Interview study if I choose not to be involved. ☐

4. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from Sponsor (The Newcastle upon Tyne Hospitals NHS Foundation Trust) or its representatives, or from regulatory or ethical authorities where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

5. I understand and agree to the interview being recorded. ☐

6. I understand that I can ask for the recording to be stopped at any time without giving a reason. ☐

7. I understand that I will not be personally named in any report and that anything I say will be treated with confidence. ☐

8. I understand that any information collected will be kept in a secure way and that all data will be anonymised so that my name does not appear. ☐

9. I understand that information collected will be managed by the study team only and will be destroyed after a period of fifteen years. ☐

10. I agree to take part in an interview for the study. ☐

Name of participant	Date	Signature
Name of person taking consent (if different from PI)	Date	Signature
Principal Investigator	Date	Signature

When completed: one copy to participant; one copy for hospital record; original copy to Site Investigator File.

Appendix 2 Adverse Event Form (Example)

Visit Number	Site Number	Recipient's Initials	Recipient's I.D.

Please record details of all new adverse events, AEs which have increased severity, changes in relationship to study treatment and all medical conditions present at study treatment initiation which have worsened. ***If the subject has not experienced any adverse events please enter "NONE".***

	Serious **0 = No** **1 = Yes**	**Adverse Event**	**Severity** **1 = Mild** **2 = Moderate** **3 = Severe**	**Relationship to treatment** **0 = Not Related** **1 = Possibly Related** **2 = Probably Related**	**Dates** **Start**	**If continuing**	**Stop**	**Action Taken** ***(enter all applicable)*** **0** = No action taken **1** = Treatment adjusted/interrupted **2** = Treatment discontinued **3** = Concomitant Medication **4** = Non-drug therapy given **5** = Hospitalisation
1					Day Month Year		Day Month Year	
2					Day Month Year		Day Month Year	
3					Day Month Year		Day Month Year	
4					Day Month Year		Day Month Year	
5					Day Month Year		Day Month Year	
6					Day Month Year		Day Month Year	
7					Day Month Year		Day Month Year	

Definitions	
Mild	Discomfort is noticed, but there is no disruption of normal daily activities.
Moderate	Discomfort is sufficient to reduce or affect normal daily activities.
Severe	Discomfort is incapacitating, with inability to work or to perform normal daily activities.

Name of person completing form: ……

Signature: ……

Date of completion

Day Month Year

Appendix 3 SF-36 Questionnaire

SF-36 QUESTIONNAIRE

(1992 -- Medical Outcomes Trust)

Patient Name: _____ **Date:** _____

1. In general, would you say your health is: (circle one)

   Excellent Very good Good Fair Poor

2. Compared to one year ago, how would you rate your health in general now? (circle one)

   Much better now than one year ago.

   Somewhat better now than one year ago.

   About the same as one year ago.

   Somewhat worse than one year ago.

   Much worse than one year ago.

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? (Mark each answer with an **X**)

ACTIVITIES	**Yes, Limited A Lot**	**Yes, Limited A Little**	**No, Not Limited At All**
a. **Vigorous activities,** such as running, lifting heavy objects, participating in strenuous sports			
b. **Moderate activities,** such as moving a table, pushing a vacuum cleaner, bowling, or playing golf			
c. Lifting or carrying groceries			
d. Climbing **several** flights of stairs			
e. Climbing **one** flight of stairs			
f. Bending, kneeling or stooping			
g. Walking **more than a mile**			
h. Walking **several blocks**			
i. Walking **one block**			
j. Bathing or dressing yourself			

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? (Mark each answer with an **X**)

	YES	NO
a. Cut down on the **amount of time** you spent on work or other activites		
b. **Accomplished less** than you would like		
c. Were limited in the **kind** of work or other activities		
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)		

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? (Mark each answer with an **X**)

	YES	NO
a. Cut down the **amount of time** you spent on work or other activities		
b. **Accomplished less** than you would like		
c. Didn't do work or other activities as **carefully** as usual		

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors or groups? (circle one)

Not at all Slightly Moderately Quite a bit Extremely

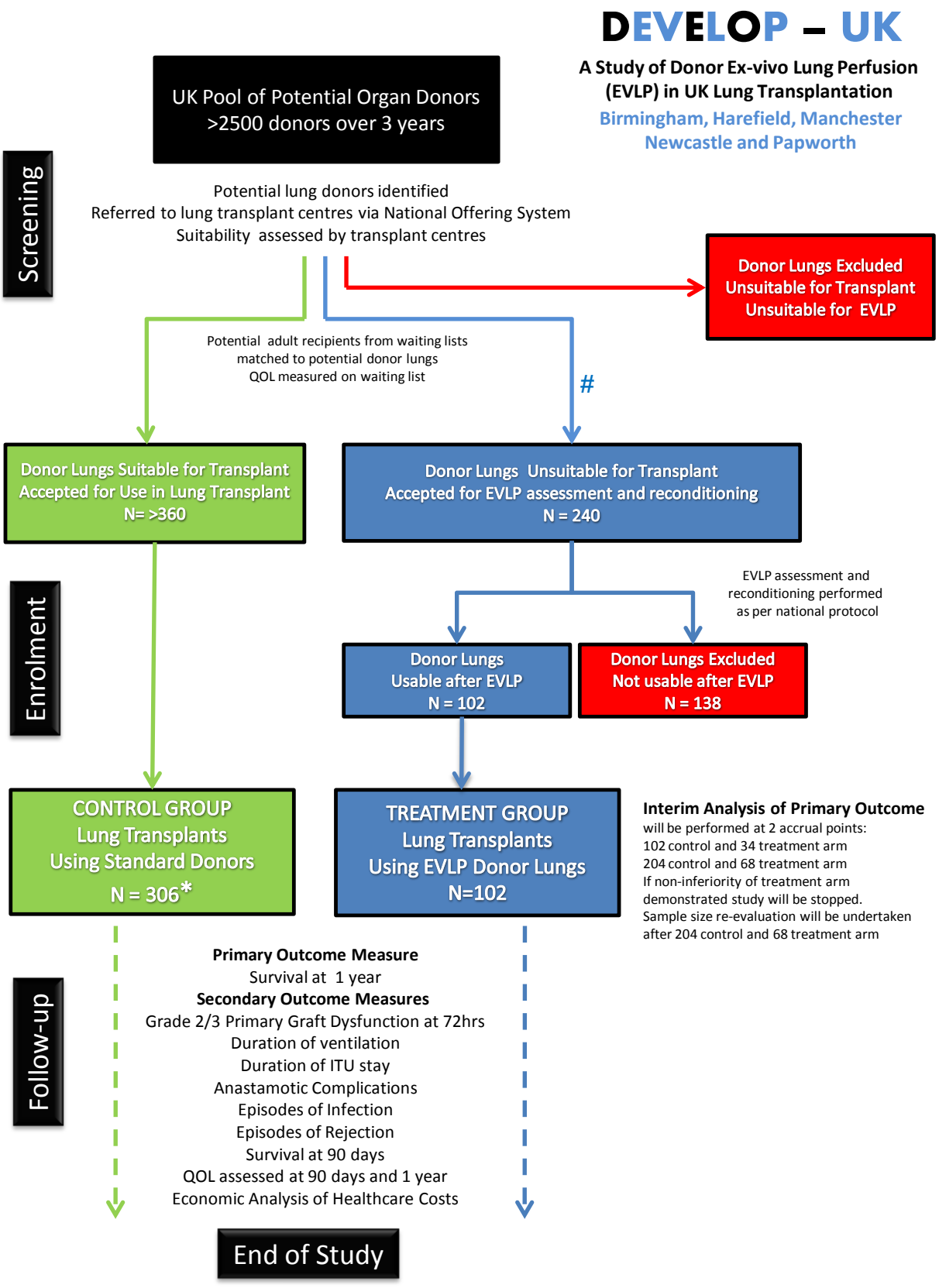
7. How much bodily pain have you had during the past 4 weeks? (circle one)

None Very mild Mild Moderate Severe Very severe

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all A little bit Moderately Quite a bit Extremely

Appendix 4 Patient Flow diagram



Appendix 5 Couraud Classification of Anastomotic Healing

Couraud Classification of Anastomotic Healing

Grade 1 Complete circumferential primary mucosal healing

Grade 2A Complete circumferential primary healing of the airway wall without necrosis and partial mucosal healing

Grade 2B Complete circumferential primary healing of the airway wall without necrosis but no primary mucosal healing

Grade 3A Limited necrosis

Grade 3B Extensive necrosis

Appendix 6 Trial Steering Committee Terms of Reference

The Trial Steering Committee (TSC) will consist of:

- Independent Chair: Dr Duncan Young
- Committee member: Professor Dirk Van Raemdonck
- Independent statistician: Dr Chris Weir
- Independent Trials Methodologist: Dr Chris Rogers
- Surgical Lead and Co-Investigator: Ms Karen Redmond
- Independent Health Economist: Dr Paul McNamee
- Lay member: Mr Chris Wiltsher
- Lay member: Ms Lesley Costello
- Chief Investigator: Professor Andrew Fisher
- Trial Statistician: Dr Thom Chadwick
- Trial Manager: Jessica Qian
- Senior Trial Manager: Dr Jennifer Wilkinson

Overall role of the TSC

The role of the TSC is to provide overall independent supervision for a trial on behalf of the Trial Sponsor and Trial Funder and to ensure that the trial is conducted to rigorous standards. The safety, rights and well-being of the trial participants are paramount.

Specific roles and responsibilities

1. The responsibility for calling and organising TSC meetings lies with the chief investigator in association with the chair of the TSC.
2. The TSC will meet at least once a year during the running of this three years and nine months trial but additional meetings can be convened if considered necessary.
3. Meetings will be minuted by the project team.
4. Minutes must be made available to the trial sponsor (The Newcastle upon Tyne Hospitals NHS Foundation Trust) and funder (NIHR HTA) if required.
5. The project team will provide the TSC with a trial report in advance of any meetings.
6. The content of the trial report will focus on trial progress and conduct.
7. The TSC chairperson will be responsible for conduct of TSC meetings and communication with the Trial Management Group (TMG).
8. In the case of a major decision, every effort should be made for the TSC to reach a unanimous decision. If the committee cannot reach a decision, a vote may be taken. If necessary, the chairperson has the deciding vote.
9. The TSC will also:
    a. receive and action feedback or recommendations from the DMEC
    b. comment on and approve any proposed substantial amendments to the trial
    c. comment on and approve the trial results dissemination strategy
    d. oversee the timely reporting of the trial results
10. Any decisions or recommendations made by the TSC will be communicated to the TMG by the TSC chairperson.
11. Any recommendation of the DMEC to discontinue or temporarily suspend study recruitment will be immediately enacted by the TSC/TMG.

Appendix 7 Data Monitoring and Ethics Committee Terms of Reference

The Data Monitoring and Ethics Committee (DMEC) will consist of:

- Independent Chair: Professor Marcus Flather
- Independent Statistician: Professor Sue Todd
- Independent Expert Clinician: Dr Paul Aurora

Overall role of the DMEC

The role of the DMEC is to monitor data and make recommendations to the Trial Steering Committee (TSC) on whether there are any ethical or safety reasons why the trial should not continue. The safety, rights and well-being of the trial participants are paramount.

Specific roles and responsibilities

1. The responsibility for calling and organising DMEC meetings lies with the chief investigator in association with the chair of the DMEC.
2. The DMEC will meet at least once a year during the running of this three years and nine months trial but additional meetings can be convened if considered necessary.
3. Meetings may take the format of open and closed session. Members of the Trial Management Group (TMG)/project team may be present for open sessions, but only independent members of the DMEC may be present for closed session.
4. Meetings will be minuted by the project team excepting any closed session which should be minuted by an independent member of the DMEC.
5. Minutes must be made available to the trial sponsor (The Newcastle upon Tyne Hospitals NHS Foundation Trust) and funder (NIHR HTA) if required.
6. The project team will provide the DMEC with a trial report in advance of any meetings.
7. The trial report will document trial progress and provide descriptive data.
8. In addition to review of the trial reports, the DMEC will review reports of all serious adverse events provided.
9. The DMEC chairperson will be responsible for conduct of DMEC meetings and communication with the TMG/TSC.
10. In the case of a major decision, every effort should be made for the DMEC to reach a unanimous decision. If the committee cannot reach a decision, a vote may be taken. If necessary, the chairperson has the deciding vote.
11. The decision made by the DMEC will usually be one of:
    a. Trial should continue as planned
    b. Trial recruitment should be suspended pending…
    c. Trial recruitment should be discontinued due to…
12. Any decisions or recommendations made by the DMEC will be communicated to the TSC and TMG by the DMEC chairperson.
13. Any recommendation of the DMEC to discontinue or temporarily suspend study recruitment will be immediately enacted by the TSC/TMG and notified to the sponsor, funder and REC using the appropriate channels.
14. Any recommendation of the DMEC to discontinue or temporarily suspend study recruitment will be followed as soon as possible by a meeting of the DMEC with the TSC and TMG to discuss the basis for the recommendation.

Appendix 8 Focussed Interview Guide

As we do not know what patients think about EVLP and research related to people's experiences of receiving donor organs is also limited, the aim of this embedded interview sub-study is to identify, describe and understand patients' pre and postoperative perceptions of EVLP, and to explore how these are affected by individual, social, physical and clinical factors.

Focussed interviews will be conducted with individuals, these are particularly useful when researching a new area about which relatively little is known. They are flexible enough to allow interviewer and interviewee to explore issues which are pertinent to the individual person and which were not anticipated in advance, thus enabling a fuller understanding of the subject under discussion. In order to explore and understand patients' views, experiences and understandings of EVLP the interviews will cover the following topics:

Preoperative interviews :

1. **Experiences of their own health and experience of living with their condition**
   Possible prompts:
   Impact on their own life (personal life/work)
   Impact on lives of significant others

2. **Experiences of waiting for a lung transplantation**
   Possible prompts:
   When were they put on a transplant waiting list
   Impact of this experience on self and others
   Sources of support

3. **Understandings of EVLP and the perceived acceptability of this procedure in comparison with other donor lungs**
   Possible prompts:
   Previous awareness/knowledge of EVLP
   Explanation of how this process differs from standard treatment
   What they considered when taking part in the study
   Other people involved in deciding to take part in the study

4. **Hopes and expectations for EVLP**
   Possible prompts:
   Hopes for selves