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National Institute for Health Research

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Disclaimer: This report contains transcripts of interviews conducted in the course of research and contains language that may offend some readers.

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Abstract

An observational study of Donor Ex Vivo Lung Perfusion in UK lung transplantation: DEVELOP-UK

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Background: Many patients awaiting lung transplantation die before a donor organ becomes available. Ex vivo lung perfusion (EVLP) allows initially unusable donor lungs to be assessed and reconditioned for clinical use.

Objective: The objective of the Donor Ex Vivo Lung Perfusion in UK lung transplantation study was to evaluate the clinical effectiveness and cost-effectiveness of EVLP in increasing UK lung transplant activity.

Design: A multicentre, unblinded, non-randomised, non-inferiority observational study to compare transplant outcomes between EVLP-assessed and standard donor lungs.

Setting: Multicentre study involving all five UK officially designated NHS adult lung transplant centres.

Participants: Patients aged ≥ 18 years with advanced lung disease accepted onto the lung transplant waiting list.

Intervention: The study intervention was EVLP assessment of donor lungs before determining suitability for transplantation.

Main outcome measures: The primary outcome measure was survival during the first 12 months following lung transplantation. Secondary outcome measures were patient-centred outcomes that are influenced by the effectiveness of lung transplantation and that contribute to the health-care costs.

Results: Lungs from 53 donors unsuitable for standard transplant were assessed with EVLP, of which 18 (34%) were subsequently transplanted. A total of 184 participants received standard donor lungs. Owing to the early closure of the study, a non-inferiority analysis was not conducted. The Kaplan–Meier estimate of survival at 12 months was 0.67 [95% confidence interval (CI) 0.40 to 0.83] for the EVLP arm and 0.80

(95% CI 0.74 to 0.85) for the standard arm. The hazard ratio for overall 12-month survival in the EVLP arm relative to the standard arm was 1.96 (95% CI 0.83 to 4.67). Patients in the EVLP arm required ventilation for a longer period and stayed longer in an intensive therapy unit (ITU) than patients in the standard arm, but duration of overall hospital stay was similar in both groups. There was a higher rate of very early grade 3 primary graft dysfunction (PGD) in the EVLP arm, but rates of PGD did not differ between groups after 72 hours. The requirement for extracorporeal membrane oxygenation (ECMO) support was higher in the EVLP arm (7/18, 38.8%) than in the standard arm (6/184, 3.2%). There were no major differences in rates of chest radiograph abnormalities, infection, lung function or rejection by 12 months. The cost of EVLP transplants is approximately £35,000 higher than the cost of standard transplants, as a result of the cost of the EVLP procedure, and the increased ECMO use and ITU stay. Predictors of cost were quality of life on joining the waiting list, type of transplant and number of lungs transplanted. An exploratory model comparing a NHS lung transplant service that includes EVLP and standard lung transplants with one including only standard lung transplants resulted in an incremental cost-effectiveness ratio of £73,000. Interviews showed that patients had a good understanding of the need for, and the processes of, EVLP. If EVLP can increase the number of usable donor lungs and reduce waiting, it is likely to be acceptable to those waiting for lung transplantation. Study limitations include small numbers in the EVLP arm, limiting analysis to descriptive statistics and the EVLP protocol change during the study.

Conclusions: Overall, one-third of donor lungs subjected to EVLP were deemed suitable for transplant. Estimated survival over 12 months was lower than in the standard group, but the data were also consistent with no difference in survival between groups. Patients receiving these additional transplants experience a higher rate of early graft injury and need for unplanned ECMO support, at increased cost. The small number of participants in the EVLP arm because of early study termination limits the robustness of these conclusions. The reason for the increased PGD rates, high ECMO requirement and possible differences in lung injury between EVLP protocols needs evaluation.

Trial registration: Current Controlled Trials ISRCTN44922411.

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List of abbreviations

ABG	arterial blood gas
AE	adverse event
BAL	bronchoalveolar lavage
BNF	*British National Formulary*
CF	cystic fibrosis
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CTIMP	clinical trial of investigational medicinal product
DBD	donation after brain death
DCD	donation after circulatory death
DEVELOP-UK	Donor Ex Vivo Lung Perfusion in UK lung transplantation
ECG	electrocardiography
ECMO	extracorporeal membrane oxygenation
EOI	expression of interest
EVLP	ex vivo lung perfusion
FBC	full blood count
FEV_1	forced expiratory volume in 1 second
FiO_2	fraction of inspired oxygen
FVC	forced vital capacity
GP	general practitioner
HDU	high-dependency unit
HLA	human leucocyte antigen
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
IL-10	interleukin 10
iLA	interventional lung assist
INSPIRE	International Randomized Study of the TransMedics Organ Care System for Lung Preservation and Transplantation
IQR	interquartile range
ISD	Information Services Division
ISHLT	International Society for Heart and Lung Transplantation
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITU	intensive therapy unit
MCS	mental component score
NHSBT	NHS Blood and Transplant
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NOVEL	NOrmothermic ex Vivo lung perfusion as an assessment of Extended/marginal donor Lungs
NuTH	Newcastle upon Tyne Hospitals
OCS	Organ Care System
PaO_2	partial pressure of oxygen
PCS	physical component score
PGD	primary graft dysfunction
PI	principal investigator
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
R&D	research and development
SAE	serious adverse event
SD	standard deviation
SF-36	Short Form questionnaire-36 items

SF-6D	Short Form questionnaire-6 Dimensions	SOP	standard operating procedure
SNOD	specialist nurse for organ donation	THAM	trometamol

Plain English summary

Donor lungs are frequently found to be unsuitable for transplantation. Ex vivo lung perfusion, known as EVLP, is a process that involves circulating a nutrient solution through the lungs, and attaching them to a ventilator machine once they have been removed from the donor. EVLP allows unsuitable donor lungs to be assessed outside the body to see if their function can be improved to make them suitable for transplantation.

The Donor Ex Vivo Lung Perfusion in UK lung transplantation study was designed to test if EVLP could safely increase lung transplant activity at an acceptable cost to the NHS. The aim was to find out if patients transplanted with a perfused donor lung were as likely to survive for 1 year after surgery as those receiving standard donor lungs. A total of 53 donor lungs were assessed ex vivo and 18 were transplanted. Twelve patients (67%) were alive after 1 year, compared with 80% of 184 patients who received standard donor lungs.

Patients who received an EVLP transplant had longer intensive care stays and needed more specialist support of the lungs, but recovered at a similar time to the standard transplant group. A lung transplant performed using perfused lungs costs about £35,000 more than a standard transplant. In addition to the type of transplant, an important determinant of cost was quality of life when an individual joined the waiting list. Those who received perfused lungs waited less time for a transplant, and patients felt that this was an acceptable technology to use. An exploratory model estimated the cost-effectiveness, and the results suggested that incorporating EVLP lung transplants into the NHS lung transplant service would not be cost-effective, as we found that the rate of converting lungs from unsuitable to suitable for transplant was low and that the rate of complications after transplantation was high.

The deaths that occurred after EVLP were not directly related to the perfusion process; they were due to recognised complications that can occur in any lung transplant patient. The small number of patients transplanted with perfused lungs compared with the number who received standard lungs limits conclusions, but the technique did improve access to lung transplant at an increased cost.

Further research is needed to improve the way in which suitability of donor lungs for EVLP reconditioning is decided and to assess why there is higher risk after transplanting EVLP donor lungs.

Scientific summary

Introduction

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. However, 20–30% of patients waiting for lung transplantation will die before a donor organ becomes available. Although a shortage of multiorgan donors contributes, the main problem is that donor lungs are very susceptible to dysfunction, and about 80% of potential donor lungs in the UK are deemed unusable for transplantation. It has 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; many centres worldwide have thus increased activity by accepting more 'extended criteria' donors. This strategy, however, is not without risks to early outcomes. The major early cause of death after lung transplantation is primary graft dysfunction (PGD), a severe lung injury akin to acute respiratory distress syndrome. Evidence that PGD has a major impact on survival comes from experience in several centres worldwide and from the International Society for Heart and Lung Transplantation: the reported incidence of PGD is up to 25%, and PGD is associated with a 30-day mortality of 50%, compared with < 10% among those without PGD. 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 donor lungs that are unusable because of poor or uncertain function 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 proinflammatory 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 that are not suitable for transplantation either because poor function is a result of irreversible damage or because pre-existing lung disease, such as emphysema, is identified in the donor lung. In this respect, EVLP may provide reassurance to potential recipients that 'extended criteria' donor lungs that might have been previously considered unusable are acceptable for lung transplantation.

As of June 2011, approximately 25% of the world's early experience with EVLP, 17 out of 65 cases, had been gained in the UK. Although initial experience was promising, a large-scale trial of the procedure was felt to be required to demonstrate its effectiveness in increasing lung transplant activity in a safe and cost-effective way. The Donor Ex Vivo Lung Perfusion in UK lung transplantation (DEVELOP-UK) study was therefore 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.

Objective

The aim of DEVELOP-UK was to evaluate the clinical effectiveness and cost-effectiveness of the 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, the study allowed the applicability of EVLP to lung transplant services in the UK NHS to be determined.

The study was designed as a multicentre, unblinded, non-randomised, non-inferiority observational study, with an adaptive design to evaluate the clinical and economic effectiveness of EVLP in assessing and reconditioning donor lungs for transplantation compared with standard lung transplantation. The study also included an embedded qualitative substudy to determine the experiences of, and hopes and fears around, EVLP use in patients waiting for, or after, lung transplantation.

As a UK-based multicentre study, it involved 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.

Methods

The target population for the study was adult patients (aged $\geq$ 18 years) with advanced lung disease who had already been accepted (at study inception) onto an active lung transplant waiting list in one of the five UK centres, plus any new adult patients who were added to the active waiting list during the course of the study recruitment from 1 April 2012 to 9 July 2014. The experimental intervention was EVLP. EVLP was performed outside the donor and recipient bodies by connecting the lungs to a semiautomated EVLP machine (Vivoline Medical AB, Lund, Sweden), which warmed lungs to body temperature and circulated a specialised perfusate solution through their vasculature. Following slow rewarming to 32 °C, the lungs were ventilated with supplementary oxygen by connecting them to a standard intensive therapy unit (ITU) ventilator. EVLP provides the opportunity to carefully assess donor lung function, including gas exchange, over a number of hours before making a decision on their usability for transplantation. The study was commenced using a hybrid EVLP protocol, combining elements of the EVLP protocols previously developed in Toronto and Lund. After 22 EVLP assessments using the hybrid protocol and following an interim evaluation of some early adverse events after the first eight EVLP transplants, the protocol was changed entirely to the Lund protocol for the remaining 31 EVLP assessments and subsequent 10 transplants.

When a lung suitable for potential transplantation became available, the NHS Blood and Transplant organ retrieval team was dispatched to the donor hospital to assess the donor lungs. After careful assessment, a decision was made using study criteria whether the lungs could be used immediately for standard transplantation, should undergo EVLP assessment and reconditioning, or were unsuitable for transplantation.

The primary outcome measure was survival during the first 12 months following lung transplantation. Secondary outcomes were clinically relevant patient-centred outcomes that are influenced by the effectiveness of lung transplantation, and that contribute to the health-care costs, impact on recipients' quality of life and cost-effectiveness.

Results

A total of 487 patients from the UK lung transplant waiting list either completed an expression of interest (EOI) form, or fully consented to participate in the study. EOI forms allowed those living a significant distance from the transplant centre to confirm their interest in participating without the need for face-to-face interaction with the research team.

Donor lungs from 53 donors deemed unsuitable for standard transplantation were assessed with EVLP, of which 18 (34%) were transplanted, constituting the EVLP arm of the study. A total of 184 patients received standard donor lungs and constitute the control arm of the study. Other than a higher proportion of donation after circulatory death and of male donors in the EVLP arm, there were no differences in the donor or recipient characteristics between the two arms.

The study did not reach target recruitment: only 184 standard transplants out of a target of 206 (60.1%), and only 18 EVLP transplants out of a target of 102 (17.6%), were achieved before the independent Trial Steering Committee advised that the study should be stopped early. This was because of poor enrolment in the EVLP arm, and because there was no indication that the rate of EVLP assessments was increasing sufficiently. In addition, there was a signal of a higher rate of serious adverse events, mainly requirement for unplanned extracorporeal membrane oxygenation (ECMO) support in the EVLP arm. The final EVLP sample size limited the subsequent comparisons to mainly descriptive statistics.

The Kaplan–Meier estimate of survival at 12 months was 0.67 [95% confidence interval (CI) 0.40 to 0.83] for the EVLP arm and 0.80 (95% CI 0.74 to 0.85) for the standard arm. Based on Cox regression, the hazard ratio for overall survival in the EVLP arm relative to the standard arm over the 12-month follow-up was 1.96 (95% CI 0.83 to 4.67).

The median duration of invasive ventilation in the EVLP arm was 72 hours, and the median ITU stay was 14.5 days. In the standard arm, the corresponding values were 38 hours and 4.3 days. Overall, post-operative hospital stay was similar in the two arms. The rate of grade 3 PGD at 24 hours was 44.4% in the EVLP arm and 17.8% in the standard arm. The rates decreased in both arms by 72 hours, to 27.8% versus 22.5%. ECMO support was required in 7 of 18 (38.8%) transplant recipients in the EVLP arm, and in 6 of 184 (3.2%) recipients in the standard arm.

There were no anastomotic complications in the EVLP arm, but 14 of 146 (9.5%) transplants in the standard arm exhibited anastomotic complications by 12 months, including two instances of bronchial dehiscence. Rates of chest radiograph abnormalities over the 12-month follow-up period were similar in the two arms, and there was a trend towards lower rates of infection in the EVLP arm. Lung function tests were similar between the groups during 12 months of follow-up. The risk of rejection was highest in the first 3 months, but there was no difference between rates of A2 rejection in the two arms of the study.

The median waiting time from listing was 197 days [interquartile range (IQR) 95–373 days] for a standard transplant and 142 days (IQR 60–199 days) for those receiving an EVLP-evaluated donor.

Owing to the small numbers in the EVLP arm of the study, the economic analysis was limited to a within-trial analysis, and the two transplant procedures were not compared directly in terms of their cost-effectiveness. The total cost of lung transplant in the EVLP arm was estimated to be around £98,186 [standard deviation (SD) £60,231]. The cost of a standard transplant was £63,637 (SD £44,047). The mean cost of the EVLP procedure itself was £14,066. The variability in the total EVLP cost is marked, with a SD in costs of £60,231. This is because of the increased use of ECMO and the increased length of ITU stay after EVLP transplant. The total quality-adjusted life-years (QALYs) gained per EVLP recipient were estimated to be 0.527 and 0.533 in the standard arm. A regression model on cost identified three statistically significant predictors of increased total cost: (1) higher quality of life when the person joined the waiting list; (2) use of EVLP procedure; and (3) transplanting two lungs (as opposed to one). An exploratory model compared a NHS lung transplant service that included both EVLP and standard lung transplants with one that included only standard lung transplants. The incremental cost per QALY was £73,000, well above values normally considered acceptable to the NHS. There was, however, considerable uncertainty around these results.

A total of 44 interviews were conducted with 24 men and 20 women, aged 21–69 years. The qualitative study suggests that patients had a good understanding of the need for, and the processes of, EVLP, although clinicians may want to consider exploring different ways and modes of providing information, depending on patient preferences. Overall, this work suggests that if EVLP can increase the number of suitable donor lungs available and reduce waiting times, then it is likely to be regarded as an acceptable technology to patients waiting for lung transplantation in the UK.

Conclusions

Overall, one-third of the donor lungs found unsuitable for standard transplantation that were subjected to EVLP in the study were subsequently deemed suitable for transplant. Estimated survival over 12 months in this EVLP group was lower than in the standard lung transplant group, but the data were also consistent with no difference in survival between groups. These additional EVLP transplants were associated with a higher rate of early severe graft injury and need for unplanned ECMO support, and were, on average, more costly. However, limited data mean that comparisons should be treated cautiously; the small number of participants in the EVLP arm (17.8% of the target), owing to slow enrolment in the EVLP arm and early study termination, limits the robustness of conclusions drawn, and results must be interpreted with caution.

Implications for practice

The DEVELOP-UK study is the first to report poorer outcomes in a group of EVLP transplants than in a contemporaneous standard lung transplant group, but few data were available for comparison. The study is the first non-commercial, multicentre EVLP study performed, and relied on a small number of centres in a single country to deliver a substantial target of EVLP assessments and subsequent EVLP transplants. To date, two commercially funded multicentre EVLP studies have been performed but have not yet fully published their results.

The slow enrolment into the EVLP arm of the study was because of a combination of the low number of EVLP assessments performed and the low conversion rate from EVLP assessment to transplant. This demonstrates the challenge of running an EVLP assessment service alongside an active clinical transplant programme when logistics and staff availability, due to competing transplant activity, can significantly affect units' ability to perform EVLP assessments.

The higher rate of early PGD grade 3 and need for ECMO support in the EVLP arm has raised issues about the selection of the best lungs on which to perform EVLP. Although there was a much higher ECMO rate, it was not associated with a higher mortality risk in the recipients undergoing ECMO, which, in most cases, was limited to a few days of support. The almost uniform use of cardiopulmonary bypass in recipients of EVLP donor lungs (89%) may also have contributed to the high early PGD grade 3 rates and the frequent use of ECMO as a second hit to donor lungs that already have disrupted vascular integrity.

Implications for research

The findings of the DEVELOP-UK study will help to direct further research in the area of EVLP. The high rate of early severe PGD and need for ECMO in this study makes it necessary to further investigate whether or not a combination of EVLP followed by transplant surgery on cardiopulmonary bypass causes a second hit that increases vascular leak and early reperfusion injury.

There is also work to be done to explore why only 30–40% of the lungs perfused in this study satisfied transplant criteria, and whether this was a problem with donor organ selection for EVLP or a result of the rigidity of following a multicentre prospective study protocol, which imposes stricter decision-making than would happen in a single centre outside of a formal study setting.

Trial registration

This trial is registered as ISRCTN44922411.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Introduction and background

Introduction

Respiratory diseases account for one in five deaths in the UK.[1] 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 (CF) lung disease, median survival after lung transplant now exceeds 10 years. However, 20–30% of patients waiting for lung transplantation will die before a donor organ becomes available. Although a shortage of multiorgan donors contributes, the main problem is that in multiorgan donors lungs are 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 to increase the numbers of lung transplants performed,[2] and many centres worldwide have increased donor lung use by accepting more 'marginal' or 'extended criteria' donors. This, however, is not without risks to early post-transplantation outcomes.[3] The major early cause of death after lung transplantation is primary graft dysfunction (PGD), a severe lung injury akin to acute respiratory distress syndrome. Evidence that PGD has a major impact on survival comes from experience in several centres worldwide,[4] and from the International Society for Heart and Lung Transplantation (ISHLT); the reported incidences of PGD are up to 25%, and PGD is associated with 30-day mortality of 50%, compared with < 10% among those without PGD.[5] 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.

Background

Ex vivo lung perfusion (EVLP) is a novel technique in which donor lungs that are unusable because of poor or uncertain function 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, as seen in *Figure 1*, 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 that are not suitable for transplantation either because poor function is a result of 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 previously have been considered unusable are now acceptable for lung transplantation.

As of June 2011, approximately 25% of the world's early experience with EVLP, 17 out of 65 cases, had been gained in the UK. Although initial experience has been very promising, a large-scale trial of the procedure was required to demonstrate its effectiveness in increasing lung transplant activity in a safe and cost-effective way.

The Donor Ex Vivo Lung Perfusion in UK lung transplantation (DEVELOP-UK) study was therefore 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 was to evaluate the clinical effectiveness 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, the DEVELOP-UK study would allow the applicability of EVLP to lung transplant services in the NHS to be determined.

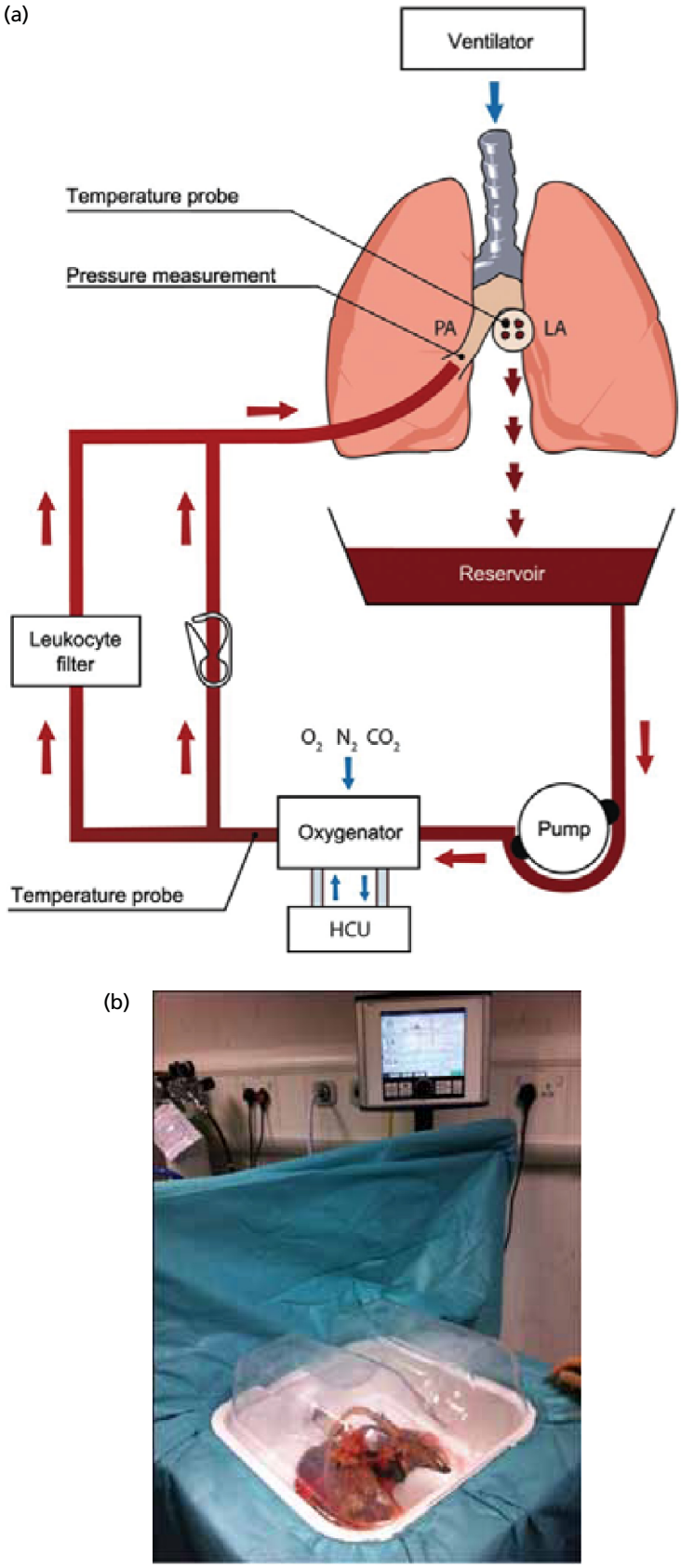

FIGURE 1 Schematic diagram of an EVLP circuit. HCU, heater cooler unit; LA, left atrium; PA, pulmonary artery. (a) A line diagram of an EVLP circuit; and (b) a donor lung undergoing EVLP on the Vivoline LS1 system (Vivoline Medical AB, Lund, Sweden). Reproduced from Wallinder *et al.*, Early results in transplantation of initially rejected donor lungs after ex vivo lung perfusion: a case-control study. *Eur J Cardiothorac Surg* 2014;**45**:40–4, by permission of the European Association for Cardio-Thoracic Surgery.[6]

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 because of the dysfunction that develops in the hours or days leading up to the donor's death. Korovesi *et al.*[7] observed that pulmonary and systemic inflammation occurred in patients who required mechanical ventilation for severe head injury. Characteristic changes in lung mechanics, suggesting subclinical pulmonary inflammation, also developed before the patients became eligible to be organ donors.[7] Fisher *et al.*[8] have shown that acute inflammation in the donor lung with elevated levels of interleukin 8 in donor bronchoalveolar lavage (BAL) is important in determining early outcomes after human lung transplantation.[9] These observations have subsequently been reproduced elsewhere in the world.[10] In addition, an imbalance between inflammatory interleukin 6 and anti-inflammatory interleukin 10 (IL-10) gene expression in the donor lung predicts adverse early outcomes after human lung transplantation.[11] These clinical observations have been modelled by Avlonitis *et al.*[12] using a rat model of brain death-induced donor lung injury and subsequent rat lung transplantation. 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.[13] Other animal models of lung transplantation have demonstrated that adenoviral gene therapy to upregulate expression of the anti-inflammatory cytokine IL-10 in the donor lung downregulates inflammation and improves function in the recipient animal after transplant.[14–17] These observations suggest that attenuating the donor lungs' inflammatory response before implantation may improve early outcome after lung transplantation, and help to safely maximise lung use from the existing donor pool.

Assessment of donor lung usability

Assessing whether or not potential donor lungs are usable for transplantation is a process that takes into consideration available donor history, subjective evaluation of chest radiograph appearance, bronchoscopy and more exact physiological data such as arterial blood gases (ABGs) following high-concentration oxygen challenge. Despite improvements in donor management practices, currently < 20% of lungs from multiorgan donors in the UK are accepted for transplantation. The internationally accepted selection criteria of the 'optimal donor' are primarily opinion based rather than evidence based, and their accuracy in determining the physiological status of the donor lung and predicting post-operative lung function is not optimal.[18] Fisher *et al.*[19] have shown that current clinical donor lung assessment criteria are poor predictors of existing inflammation or infection in the donor lung, suggesting that many donor lungs deemed unusable may be unnecessarily excluded. Ware *et al.*[20] evaluated 29 pairs of unusable lungs by physiological, microbiological and histological methods, and concluded that as many as 40% of these lungs would have been potentially suitable for transplantation. Thus, there is urgent need to improve the donor lung selection process through more objective physiological assessment; EVLP can provide a platform to achieve this. In practice, not all of the unused donor cohort will be suitable donors, as some will have absolute contraindications to lung donation, while 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, therefore, in this study, we were aiming for a 30% overall increase in lung transplant activity.

Early pathway development

Ex vivo lung perfusion 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.[21] Subsequently, porcine studies showed that maintenance of intact vascular function was achievable for up to 24 hours using EVLP, and that functioning lungs could be obtained from donors after circulatory arrest in a porcine model. The clinical EVLP technique was initially developed by Steen *et al.*[22] in Sweden to assess lungs from donation after circulatory death (DCD) 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 human DCD donor assessed by EVLP prior to successful transplantation.[22] 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.[23] This led to the first clinical report in 2007 of actual reconditioning of an unusable donor lung prior to successful lung transplantation.[24]

Clinical ex vivo lung perfusion 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.[22] The Steen group described successful reconditioning and transplantation of six out of nine donor lungs previously deemed unusable for transplant.[24] All six survived the first 3 months and four of the six were alive and well 12 months after transplant.[25] Subsequently, Cypel *et al.*[26] in Toronto modified the EVLP protocol significantly to include an acellular perfusate, a closed perfusion circuit and low perfusion pressures of no more than 40% of calculated cardiac output, and demonstrated that lungs can be maintained on EVLP for more prolonged periods with this approach.[26] This group have published their experience of the Human Ex-vivo Lung Perfusion study[27] 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 performed over the same time period, with a 15% incidence of PGD in the EVLP group and of 30% in the standard transplant group ($p = 0.11$).

The UK was the third country worldwide to perform a lung transplantation using EVLP-assessed and -reconditioned donor lungs. The first case was performed by the Manchester group, followed rapidly by the programmes in Harefield,[28] Newcastle and Cambridge. By June 2011, UK activity had totalled 17 transplants performed with lungs that would not have been used without EVLP assessment and reconditioning. The 90-day survival in these 17 cases was 100%, with one subsequent death from pneumonia at 9 months, and one further death at 18 months due to rejection. When the Swedish and UK experience was added to the Toronto experience, the findings suggested that early survival is very good, with only two deaths within 90 days among over 65 EVLP transplants. The UK experience revealed that the successful conversion rate during EVLP from unusable to usable donor organs was approximately 50%, which was lower than that reported in the Toronto experience. This may represent the high proportion of DCD donors in Toronto, where EVLP was being used primarily for assessment rather than for reconditioning.

International experience has since grown, with case series now reported by multiple groups internationally, including in Paris, Madrid, Vienna, Milan and Gothenburg, with patients successfully transplanted with EVLP lungs recovered from uncontrolled and controlled DCD donors.[29,30]

In 2010–11, the UK was in a unique position, with four of its five adult lung transplant centres having already developed clinical experience in EVLP. At that time, there had been no systematic studies powered to evaluate the clinical effectiveness, safety and cost-effectiveness of EVLP performed anywhere in the world, and this was the impetus for the UK lung transplant community to come together in a collaborative effort in the DEVELOP-UK study.

Keshavjee *et al.*, in Toronto, have, with their extensive contributions, changed the landscape of EVLP into a technique to significantly expand the limited donor pool currently used in transplant centres all around the world.[27,30–32] The focus of Keshavjee and Cypel's studies in Toronto has not been just to evaluate whether a graft is usable or not, but also to prolong the perfusion times to be able to potentially treat and better recondition injured lungs before transplantation. They have most notably revised the Lund protocol to potentially increase the option of longer-term perfusion with an acellular perfusate to avoid potential detrimental haemolysis. This is combined with a low-flow strategy with only 40% of estimated cardiac output to reduce pulmonary vascular shear stress and oedema formation, and closed circuit with both the

pulmonary artery and left atrium cannulated, creating a positive left atrium pressure. The prospective, non-randomised, multicentre study NOVEL (NOrmothermic ex Vivo lung perfusion as an assessment of Extended/marginal donor Lungs) has recently been completed in the USA with the Toronto EVLP protocol and the XPS™ system (XVIVO Perfusion AB, Gothenburg, Sweden) to approve its clinical use.

Warnecke *et al.*,[33] in 2012, investigated the effect of normothermic preservation and transportation of standard criteria human donor lungs on a portable EVLP system. Twelve pairs of standard donor lungs were, instead of being brought to their centres by means of cold preservation on ice, preserved by normothermic perfusion and ventilation on the transportable Organ Care System™ (OCS) lung (TransMedics Inc., Andover, MA, USA). This was the first report of a portable EVLP system used in clinical transplantation, with short-term outcomes shown to be non-inferior to controls.[33]

The OCS protocol used in this pilot study was a hybrid of the Lund and Toronto EVLP protocols. A cellular perfusate based on Steen Solution™ (XVIVO Perfusion AB, Gothenburg, Sweden) supplemented with erythrocytes and an open left atrium was combined with a perfusate flow limited to 2.5 l/minute, resembling the protective approach developed by the Toronto group. The OCS protocol is currently being evaluated on a larger scale in a prospective, randomised multicentre pivotal trial, OCS International Randomized Study of the TransMedics Organ Care System for Lung Preservation and Transplantation (INSPIRE), comparing transplant outcomes of standard criteria lungs preserved and transported by either normothermic EVLP or standard cold preservation.[34] Moreover, the international EXPAND (Evaluate the Safety and Effectiveness of The Portable OCS Lung For Recruiting, Preserving and Assessing Expanded Criteria Donor Lungs for Transplantation) trial was recently launched as a clinical pilot to evaluate the more traditional use of assessing and, possibly, reconditioning lungs deemed unusable for standard transplantation on the OCS lung portable system.[35]

The development of semiautomated systems with disposable kits has made conducting EVLP more standardised, and has allowed protocols to be developed, as seen in the Vivoline LS1 (Vivoline Medical AB, Lund, Sweden) in *Figure 2*. The LS1 is a semiautomated EVLP system that was used at all sites in the DEVELOP-UK study.

Ex vivo lung perfusion biological mechanisms of action

There are a number of mechanisms by which the reconditoning effects of EVLP are believed to occur. These are outlined in the following sections.

Haemodynamic factors

Controlling the speed and pressure of initial reperfusion of the transplanted lung in animal models reduces the risk of developing PGD.[28] 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 the 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 post-capillary venules and capillaries.

Protective lung ventilation

Protective lung ventilation strategies are the standard of care for intensive therapy unit (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 fraction of inspired oxygen (FiO_2)] and to employ sustained positive end expiratory pressures to overcome atelectasis

FIGURE 2 Photograph of (a) the Vivoline LS1 EVLP machine and (b) the disposable lung kit.

without deleterious effects on systemic haemodynamics. Bronchial toilet with site-directed BAL limits ventilation–perfusion mismatch, thus avoiding regional hypoxia with high pulmonary vascular resistance and parenchymal damage. Immediate results from Gram stains of BAL directs antibotic therapy, with perfusion itself reducing microbacterial load.[36]

Perfusate-related factors

One of the major mechanistic benefits of EVLP is the use of Steen Solution, an albumin- and dextran-rich perfusate solution with a high oncotic pressure. 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 leucocytes. 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 suboptimal brain death environment in the donor. Eliminating the ongoing triggers of donor lung inflammation, including the endogenous toll-like receptor ligands and activated donor leucocytes, 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.[37] Similarly, a stem cell therapy approach via EVLP has been shown to improve acute lung injury in human lungs.[38]

Chapter 2 Study rationale and design

Study design

The DEVELOP-UK study was designed as a multicentre, unblinded, non-randomised, non-inferiority observational study with an adaptive design, to evaluate the clinical and economic effectiveness of EVLP in assessing and reconditioning donor lungs for transplantation compared with standard lung transplantation. The study also includes an embedded qualitative substudy.

Primary outcome measure

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

Secondary outcome measures

The secondary outcome measures in this study were all deemed to be important, clinically relevant, patient-centred outcomes that are influenced by the effectiveness of lung transplantation, contribute to the health-care costs and impact on health-related quality of life (HRQoL).

Primary graft dysfunction 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.[39] 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 radiograph. The PGD grade has been validated in both retrospective and prospective studies, and presence of PGD grade 3 at 72 hours is associated with a reduced early survival. A full PGD score was requested to be determined for all patients in the study.

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

The presence of specific post-operative complications was also collected as a secondary outcome measure. These complications included anastomotic complications scored using the recognised and validated Couraud Classification (see *Appendix 1*),[40] which scores airway complications including dehiscence or stricture requiring dilatation or stent placement. Episodes of infection requiring treatment with or without associated hospital admission during the first year, and episodes of acute rejection of ISHLT grade A2 or higher, B1 or higher, or clinically diagnosed acute rejection requiring treatment during the first year, were also collected.

Details of lung function measurements by forced expiratory volume in 1 second (FEV_1) and vital capacity at 1, 3, 6 and 12 months post transplant were collected to demonstrate changes in lung allograft function in the first year. Data on chest radiograph appearance at the same time points as lung function were

collected to look for any persistent abnormalities such as effusions, cavitation or chronic scarring from the time of transplantation.

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

An assessment of HRQoL using the Short Form questionnaire-36 items (SF-36) was collected at three time points in the study (while participants were waiting for transplant and again at 90 days and 1 year post lung transplantation) allowing comparison of HRQoL measured while on the waiting list with that measured post transplant. The HRQoL scores have allowed health state utility scores to be determined using the Short Form questionnaire-6 Dimensions (SF-6D) as part of the economic evaluation.

Health economic assessment

In addition, the full economic impact of using EVLP-reconditioned lungs was assessed, allowing policy-makers to consider these costs in comparison with benefits of increased donor utilisation and reduced waiting list mortality. We aimed to determine whether or not EVLP is a cost-effective intervention for the NHS to support as standard care within UK lung transplant centres in the future.

Patients' attitudes and experiences

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

Predicting ex vivo lung perfusion success or failure

The DEVELOP-UK study provided 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 can therefore be correlated with the decision of whether or not to accept the donor lungs for transplant and with clinical outcomes in recipients of EVLP donor lungs.

Sample collection and storage

To add significant value to the DEVELOP-UK study, standardised protocols for BAL, perfusate and lung tissue sampling during EVLP and subsequent storage have been developed. The collection and storage of samples during EVLP was part of the DEVELOP-UK study, and allowed complementary mechanistic studies of EVLP to be performed from the data set. Details of the laboratory-based mechanistic work are, however, not included in this report, as this element of the study was funded from sources other than the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme.

Justification for non-randomised design

This is a non-randomised study, as randomisation between EVLP and standard lung transplantation was not considered a viable option. 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, human leucocyte antigen (HLA) tissue matching to avoid any pre-formed HLA antibodies in the recipient. It was,

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 his or her pre-allocated group, which would not be ethically acceptable. Randomisation would be possible only if all donor organs were being randomly allocated to EVLP or control, but this is a different research question and was not an objective of this study.

Lung donations from donors with brain death and DCD donors were considered in both arms of this study. The number of DCD donors is increasing year on year in the UK.[41] Evidence has emerged that, when lungs from these donors are transplanted, outcomes in recipients are comparable to those achieved with lungs from donation after brain death (DBD) donors.[42] However, only a fraction of the UK DCD donors, currently about 5%, have their lungs used for standard transplantation.[41] Frequently, there are 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 that 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.

It was anticipated that a direct result of the DEVELOP-UK study would be an increase in the proportion of DCD donor lungs being used, as DCD donor lungs are often deemed unusable because functional information about the organs is unavailable, which is an indication for use of EVLP assessment. It was considered likely that as the number of DCD donors increases, more lungs from this cohort of donors would be transplanted 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. To ensure that the possible higher proportion of DCD donor lungs in the EVLP arm of the study did not bias the results, we planned to use the donor type (DCD or DBD) as a covariate in the multiple regression analysis of the primary and secondary outcome measures to determine their influence.

Justification for adaptive study design

The study statistics and trial methodology teams, in consultation with the clinical investigators, made the decision to use an adaptive design for the DEVELOP-UK 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 allow for re-evaluation of the sample size requirements on the basis of a potentially improved standard of care. It was felt that a total of three analyses, two interim and one final, would achieve a suitable balance between allowing for early stopping and ensuring that sufficient data were collected on secondary outcome variables to make these meaningful. The plan was for the interim analyses to be carried out once a prespecified number of patients had been recruited to each arm (see *Power calculation and definition of non-inferiority*). The O'Brien–Fleming critical values for the analyses during our study were chosen so that the overall study would have sufficient power to detect our target differences at a significance level of 0.05 once allowance had been made for the interim analyses.

Power calculation and definition of non-inferiority

In the standard arm, the initial best available estimate for survival to 30 days was 94.2%, for survival to 90 days was 91.2% and for survival to 1 year was 78.7%. These data were determined from the Royal College of Surgeons' UK national audit of lung transplant outcomes. Our aim was to demonstrate that using reconditioned EVLP lungs does not increase the hazard rate of death during the first year by a factor of > 2. 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 1 year. It was considered that such a difference is not clinically significant and still represents an advantage over waiting longer for a transplant.

It was anticipated that over the predicted 3 years of the study, about 100 EVLP lungs would be transplanted and ≥ 300 normal lung transplants would take place. If both treatment arms matched the standard 78.7% rate of survival over 12 months, then approximately 85 deaths would occur within 1 year of transplantation. Using a fixed sample design, this would be sufficient to ensure 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.[31] The study was therefore powered to detect a difference of 2, meaning that non-inferiority is assumed to have been achieved if the hazard rate of 12-month survival is not doubled by the use of EVLP.

To obtain sample sizes for an adaptive design, we took the standard sample size and multiplied 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 was 1.0128, resulting in a sample size of 304 in the standard arm and 102 in the EVLP arm. We increased the sample size to 306 in the standard arm while keeping it at 102 in the EVLP arm so that the sample size in both arms would be divisible by 3, to allow for equally spaced interim analyses. This resulted in a required minimum total sample size of 408 with interim analyses after 12-month survival data were available from 102 and 204 patients in the standard arm (34 and 68 in the EVLP arm).

Risks and anticipated benefits for study participants, NHS 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 transplantation surgery in terms of extended longevity and improved quality of life. As a result, many patients die on the waiting list before suitable donor lungs become available. EVLP allows otherwise unusable donor lungs to be meticulously assessed and potentially reconditioned for successful transplantation. The study would also help to understand better how to optimise the 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 participant awaiting lung transplantation is that if they are enrolled in the EVLP arm they may receive a lung or lungs that do not function well, but that risk also exists for standard donor lungs accepted by the current assessment methods. Compared with standard criteria organs, it was not anticipated that EVLP should expose recipients to any different risk profile in terms of microbiological exposure, intensity of induction and maintenance immunosuppression or early post-transplant complications. This was based on reported worldwide experience with EVLP at the time (2010–11) the study was designed and launched. Patients awaiting lung transplantation have severe, often complex, morbidity and place a heavy resource 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.[43] Fewer than 20% of transplant recipients 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 to reduce the UK health- and social-care costs of patients awaiting lung transplantation. Furthermore, by assessing the economic impact of using EVLP-reconditioned lungs, the study results should allow policy-makers to balance these costs against the benefits of increased donor utilisation and reduced waiting time mortality. The study aimed to help determine if EVLP is a cost-effective use of tax-payers' money and an intervention applicable to NHS lung transplant services.

Study population

The DEVELOP-UK study was a UK national multicentre study involving all five officially designated NHS lung transplant centres: Freeman Hospital, Newcastle upon Tyne; Harefield Hospital, London; Papworth Hospital, Cambridge; Wythenshawe Hospital, Manchester; and 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 was adult patients aged ≥ 18 years with advanced lung disease, who had already been accepted (at study inception) onto an active lung transplant waiting list in one of the five UK centres, plus any new adult patients who were added to the active waiting list during the study recruitment period of April 2012 to June 2014. The full network coverage means all patients awaiting lung transplantation in the UK, at any one time approximately 250, had the opportunity to take part in the study, and our previous pilot experience suggested that > 90% would consent to take part. The study was designed to have no effect on how potential lung transplant recipients were assessed or selected, or the timing of when they were added to the active transplant waiting list. The flow chart in *Figure 3* shows the planned recruitment targets and summary of data collection for the DEVELOP-UK study.

Study inclusion criteria

Male or female adult patients (aged ≥ 18 years) who were either already on or added to the active waiting list for their first lung transplant while the DEVELOP-UK study was in its recruitment phase were eligible to participate; patients provided informed consent for participation in the DEVELOP-UK study at the time of study commencement or time of listing for transplant and reconfirmed informed consent for the DEVELOP-UK study on the day of lung transplant.

Study exclusion criteria

Patients aged < 18 years and adult patients listed for lung retransplantation, heart–lung transplantation, multiorgan transplantation including lung or live donor lobar transplantation were excluded. Patients not in possession of the patient information sheets for the DEVELOP-UK study prior to the day of lung transplantation or those not reconfirming consent for the DEVELOP-UK study on the day of lung transplant were excluded. Patients in the ITU requiring invasive ventilation, extracorporeal membrane oxygenation (ECMO) or interventional lung assist (iLA) support when a donor lung became available were excluded. Patients enrolled in other trials within the preceding 12 months of signing an expression of interest (EOI) or giving full consent had to be discussed with the principal investigator (PI) and chief investigators before being excluded on this basis.

Inclusion and exclusion criteria for interview substudy

All patients who were eligible for the DEVELOP-UK study at The Newcastle Hospitals NHS Foundation Trust and the Royal Brompton and Harefield NHS Foundation Trust were eligible for the interview study. All patients who consented to the DEVELOP-UK study, as a whole, at the above centres were eligible to take part in the interview substudy regardless of whether or not they received a transplant. All patients who consented to the DEVELOP-UK study from Manchester, Papworth and Birmingham sites were excluded from the qualitative study.

Concomitant medications

All standard prescribed medications taken by patients on the waiting list for lung transplantation were permitted in the study. Some medications are stopped at the time of transplant or in the perioperative period. These changes are in line with standard clinical processes and were felt to be equally likely to occur in lung transplant recipients in both arms of the study.

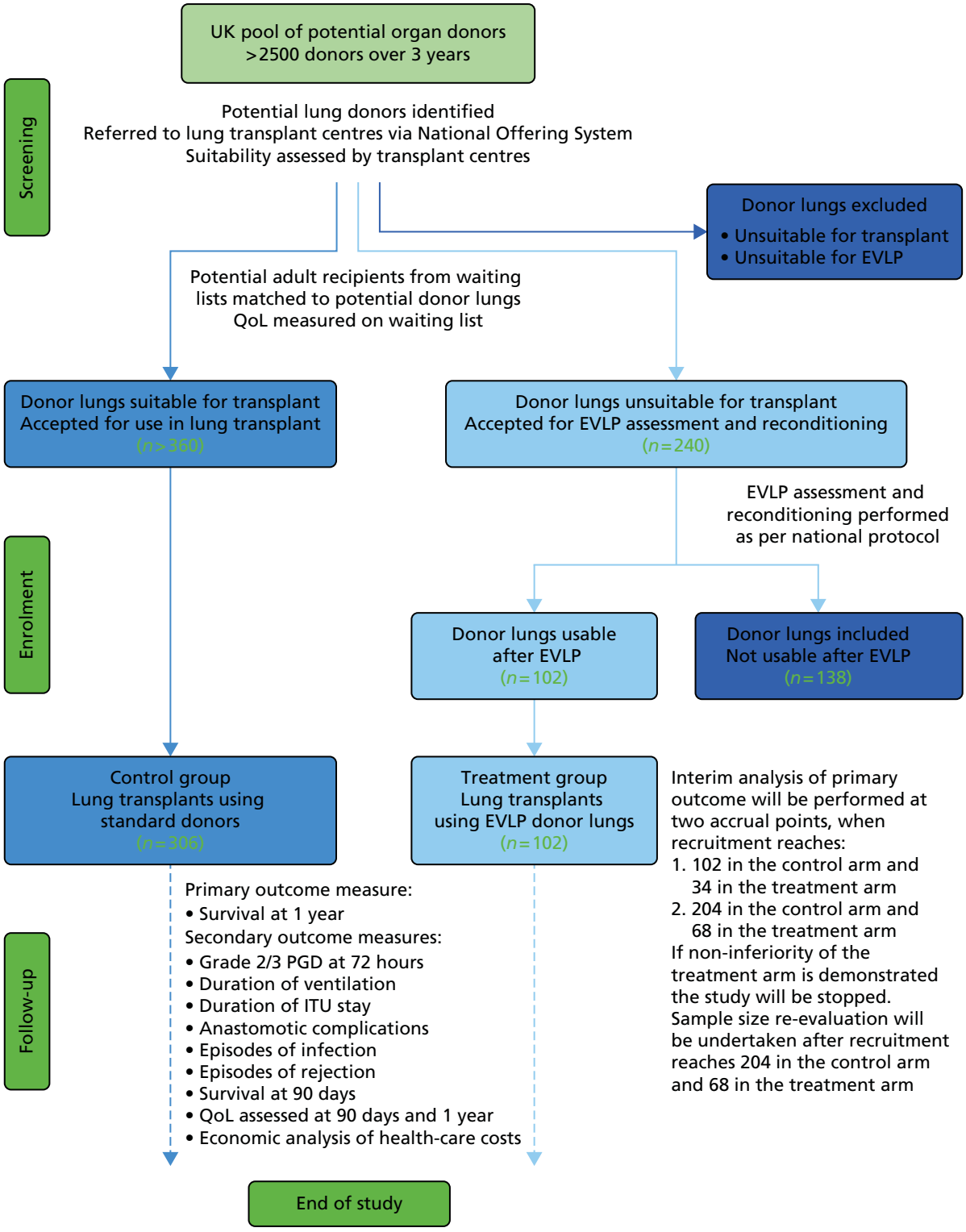

FIGURE 3 Diagram to explain planned recruitment targets, study end points and planned analysis. QoL, quality of life.

Peri- and post-transplant immunosuppression, including any induction therapy and maintenance immunosuppression, may vary slightly between centres, but continued as per usual practice during the study. In any of the centres, patients in both the EVLP and standard arms of the study got the same standard routine immunosuppressive approach normally used in that centre. The immunosuppressive regimes could, however, be changed, intensified or reduced in line with standard transplant clinical

management of the individual patient and his or her circumstances. It was possible that patients awaiting lung transplantation might already be enrolled in a clinical trial of investigational medicinal product (CTIMP) for their underlying disease. Such medications were stopped at the time of transplant and participation in the CTIMP was censored as an event and, therefore, the participation of these patients in the DEVELOP-UK study was not affected.

Patients enrolled in the DEVELOP-UK study who underwent lung transplant in either the standard or EVLP arm should not have been enrolled in any other interventional study in their first 12 months post transplant that might have an effect on 12-month survival. If there was any question of this, then the local PI discussed this with the DEVELOP-UK study chief investigator, who then liaised with the chief investigator of the other study and reported back to the trial steering committee. Observational non-interventional studies were allowable but, again, the local PI had to check with the chief investigator to make sure that there was no interference between the studies. Participants were free to be entered in interventional studies started after their first 12 months post lung transplantation.

Limiting the potential for bias

As a non-randomised, non-blinded study, it was important that the potential for bias in the selection of recipients to receive donor lungs from the EVLP or standard arms was considered and carefully monitored. There was, 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 was established before the clinical decision on the usability of the donor lungs was made, meaning that recipient selection should not be influenced by whether EVLP-conditioned or standard lung donation occurs. In particular, there was no evidence to suggest that sicker recipients, whose transplant might be seen as more urgent, would be more likely to receive EVLP-reconditioned lungs than standard donor lungs.

Only when donor lungs were available that had more than one potentially matching recipient was urgency taken into account by the transplant centre. This scenario would be likely to happen as frequently in the standard transplant arm as in the EVLP arm. The two arms of the study were monitored carefully to ensure that no systematic differences occurred in the recipient characteristics. Additionally, it was planned that recognised covariates that are known from the international registry to influence outcomes after lung transplantation would be adjusted for in the statistical analysis. Our pilot experience of transplants performed using EVLP-reconditioned lungs across the UK centres 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.

Interventions common to experimental (ex vivo lung perfusion) and control (standard) groups

Donor pathway

Any potential offer of donor lungs was communicated to the transplant centres by standard procedures via the specialist nurses for organ donation (SNODs). Each of the five centres was then responsible for making an initial assessment of the suitability of the donor lungs for transplant, and for determining if they had an appropriately matched potential recipient on their waiting list. If a centre did not have a suitably matched recipient, then the donor lungs were offered to another centre in a controlled rotational manner as part of the standard donor organ placement protocol by NHS Blood and Transplant (NHSBT). The donor lung indices were compared against the donor lung selection criteria for the study and, if suitable for potential transplantation, then the NHSBT zonal organ retrieval team were dispatched to the donor hospital to further assess the donor lungs. After careful assessment, a decision was made using the donor lung acceptance criteria whether the lungs could be used immediately for standard transplantation, should undergo EVLP assessment and reconditioning or were contraindicated completely for transplantation.

If appropriate for transplant, the donor lungs were then transported back to the transplant centres in accordance with standard practice.

Donor lung procurement for all lungs in the DEVELOP-UK study

A standard lung procurement procedure was followed for donor lungs used for EVLP in the study. In brief, the organs were antegradely flushed with supplemented PERFADEX® (XVIVO Perfusion AB, Gothenburg, Sweden) [3.3 ml of 3.6% trometamol (THAM), 0.6 ml of calcium chloride ($CaCl_2$) ± 2.5 ml of prostacyclin/l], initially at room temperature and then the remainder at 4 °C. A minimum volume of 60 ml/kg was given. After the antegrade dose, 200 ml was given down each pulmonary vein as a final retrograde flush. An adequate portion of main pulmonary artery, left atrial cuff and, particularly, at least 4 cm of trachea was taken by the retrieval surgeon.

Donor and next of kin consent

Consent for potential donor lungs to be used for lung transplantation was obtained from the donor's next of kin at the donor hospital by the SNODs, who were employed by NHSBT. This process is standardised nationally and was performed completely independently of the DEVELOP-UK study.

If standard consent for lung donation was granted, the SNODs also asked the next of kin for generic research consent, which is a standard part of the donor consent process. This allowed the study team to collect and store samples from the donor lung before and after EVLP, as described in *Appendix 2*, for parallel mechanistic studies even if the donor lungs were not deemed transplantable after EVLP. If the donor's next of kin did not provide generic research consent, then only clinical data measured during the EVLP process were collected and used in the study, and no lung tissue samples were taken for mechanistic work. This did not compromise the delivery of the primary and secondary end points of the study.

Lung recipient pathway pre and post transplantation

Patients referred to any of the five participating sites for consideration of lung transplantation over the course of the study recruitment phase underwent a standard clinical assessment. Those deemed eligible for, and who consented to, lung transplantation were added to the active lung transplant waiting list. Those on the transplant list at the time of study inception would already have been through the same assessment process.

At the time of listing for transplant, patients were offered the opportunity to take part in the DEVELOP-UK study. In addition, at the time of study inception, any patient who was already on the active lung transplant list was also offered the opportunity to take part in the DEVELOP-UK study. The consent process was performed in accordance with National Research Ethics Service guidance, as described in *Lung recipient consent*. As the period of waiting for lung transplantation can vary widely and commonly exceeds 12 months, it was necessary to reconfirm consent for the study at the time when a potential donor lung(s) became available and the study participant was called in for possible transplantation. However, if the original consent form had been signed on the day of transplant, reconfirmation of consent was not required.

Patients were told on the day of transplant whether they were to receive a donor lung that had undergone EVLP assessment and reconditioning or a standard donor lung. Patients received either standard donor lungs direct from a donor (standard transplant, control arm) or donor lungs after EVLP assessment and reconditioning (intervention arm) in accordance with 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 were thoroughly counselled prior to being accepted onto the transplant list about the need for absolute concordance with their treatment and to attend all arranged post-transplant follow-up visits. As a result, during the multidisciplinary pre-transplant assessment,

a considerable amount of time was spent explaining this aspect of care to the patients. If, despite these attempts, there remained evidence of likely non-compliance with treatment, these individuals were not usually offered the option of transplantation.

Lung recipient consent

Informed and voluntary consent was obtained via an iterative process, first at the initial discussion of the clinical and research aspects of the study, and then again, provided this occurred not less than 24 hours later, on the day of possible transplant. If, however, the consent form was signed on the day of transplant, reconsent was not required. Consent for the DEVELOP-UK study participation was 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, were required to determine eligibility for the trial element of the DEVELOP-UK study. Therefore, all adult patients being considered for lung transplant who satisfied the inclusion criteria were 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 was therefore an important consideration. The initial consent process took place well ahead of the time of transplant and the stressful environment that this generates. Consent was taken either at inception of the study for those already on the transplant waiting list or at the time of listing for transplant for those added to the active transplant list during the course of the study. A copy of the consent documentation is included in *Appendices 3* and *4*.

Consent was taken by the site PI or a member of the study team with appropriate designated responsibility on behalf of the local PI. In the consent process, care was 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 was explained; definitions of acceptability of lungs for standard transplantation and for transplantation after EVLP were agreed and standardised across all centres. Patients were offered firm reassurance that if donor lungs did not improve sufficiently after EVLP reconditioning to satisfy acceptability criteria, they would not be used. Any potential recipient who decided not to participate in the DEVELOP-UK study continued to have equal access to donor lungs for standard transplant. Those choosing not to give consent were not obliged to give a reason, but if they provided a reason this was recorded in an anonymised way to inform the Trial Steering Committee.

Additional informed consent, using a separate participant information sheet and consent form, was 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 did not preclude participation in the trial.

For both the trial and the qualitative substudy, if a potential participant had the capacity to consent for him/herself, but was unable to provide written consent because of visual or motor impairments, or literacy problems, oral informed consent was taken in the presence of an independent witness, who initialled, signed and dated the consent form on the participant's behalf.

We did not anticipate that any potential study participants would lack capacity to consent on initial recruitment to the study or at the point of reconfirming consent at the time a donor lung became available. It was, however, possible, although 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 in the ITU or by suffering a stroke, we planned 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.[44]

We did not seek separate written consent from nominated consultees in the event of loss of capacity, as this scenario was included in the initial participant consent form and patients were specifically asked to give consent for continued collection of observational data as part of the study if they lost capacity after

transplantation. As many of the data in the follow-up period were observational, their collection did not impact on the standard care that any participant who has lost capacity would expect to receive.

The original signed consent form and reconsent form were retained in the investigator site file, with a copy in the clinical notes and a copy provided to the participant. Participants were asked to consent explicitly to their general practitioner (GP) being informed of their participation in the trial element of the DEVELOP-UK study.

The right to refuse to participate without giving reasons was respected. Owing to the small subject population, the information sheet and consent form for the study were available only in English. Interpreters were available for all visits of patients who required them either for verbal translation to another language or for deaf subjects wishing to take part in the study, via local NHS arrangements.

Protocol compliance

The protocols determining the selection of donor lungs to undergo EVLP and indices that determine whether or not the lungs were suitable for transplant after EVLP were clearly described in the study protocol and are presented in an appendix to this report (see *Appendix 2*). To ensure compliance with the protocol, data were collected about the donor assessment and EVLP procedure. This allowed confirmation that the donor lung was appropriately allocated to undergo EVLP and that the decision on its suitability was correctly determined. If any instances were identified when the protocol was not followed, this was recorded as a protocol deviation and the site PI was asked to document why the protocol deviation occurred.

Ethics and regulatory issues

The conduct of this study was 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.[45] All members of the research team, the investigators and supporting staff at each of the participating sites received 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,[44] and were expected to operate to principles of good clinical practice.

A favourable ethical opinion from the National Research Ethics Service (reference number 11/NE/0342) and NHS research and development (R&D) approval was secured prior to commencement of the study. Local NHS approvals were secured before recruitment commenced at each site. The Newcastle Clinical Trials Unit, in its capacity as study co-ordination centre, obtained a written copy of local approval documentation before initiating each centre and accepting participants into the study.

Information sheets were provided to all eligible subjects, and written informed consent was obtained prior to any study procedures. Patients on the transplant waiting list who lived a significant distance from the transplant centre were given the opportunity to sign an EOI form that allowed them to subsequently consent when next attending the transplant centre (which might be on the day of transplant). Signing of the EOI form permitted completion of the first SF-36 questionnaire and collection of waiting list survival data. Copies of the patient information sheet and consent forms are included in *Appendix 4*.

We obtained informed and voluntary consent via an iterative process, providing adequate time (i.e. a period of not < 24 hours) for consideration and discussion of the clinical and research aspects of the study. For incident cases, initial consent was taken at the time a patient was listed for lung transplant. For those patients already on the transplant list at the time of study initiation, consent was sought when the study opened at their transplant centre. Reconsent on the day of transplant was sought only from patients initially consenting to the study prior to the day of lung transplant.

Assessments and data collection

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

The scheduled outpatient study visits were at 1, 3, 6 and 12 months post transplant. A window of ± 10 days around each timetabled study visit was allowed. If a participant was unable to attend a study visit within the allowable window, for example because he or she was an inpatient at an external hospital that was not the study centre, then every effort was made to acquire the same study-specific information from the non-study hospital. The HRQoL questionnaire (SF-36) was self-completed by each study participant (or in conjunction with their nominated proxy).

Patients' views and perceptions of EVLP were explored through qualitative interviews conducted by a trained researcher. When possible, these interviews were performed face to face at study visits after transplantation. Those interviewed prior to transplant were interviewed either in their own home or, more usually because of the large geographic spread of individuals, by telephone.

All clinical tests required to determine the success of EVLP assessment and reconditioning of donor lungs, including ABG analysis, glucose and lactate concentration measurement, and microbiological cultures, were performed in each study centre using local laboratories and equipment.

Standard blood profiles during follow-up were performed as part of the recipients' routine clinic care in each participating centre's certified NHS laboratories, and results were obtained from hospital data systems.

Data were collected by direct clinical observation, by clinical interpretation and from source patient records or NHS documentation by the study clinical research fellow and the study research nurse, and the required data fields were completed on the case report form (CRF) by the research nurse or a designated data manager in each centre under the supervision of the local PI. A paper CRF was initially used in the study, but in early 2014 an electronic CRF (MACRO; InferMed, Elsevier, London, UK) began to be used, in line with regulations at the sponsoring trust. The donor data required for the study (such as age, comorbidities and oxygenation, among others) were collected routinely by the SNODs, and were then captured electronically by linking to the core data data set collected by NHSBT centrally.

Serious adverse event reporting

Guidance on adverse event (AE) and serious adverse event (SAE) reporting, as well as determining the degree of relatedness and assessment of causality for SAEs that may be related to study participation, was provided in the study protocol.

As lung transplant recipients experience a significant number of AEs as part of their normal recovery from transplant surgery, the study protocol provided clear guidance on what constituted a SAE that required expedited reporting. This was to avoid a huge burden of reporting that had no relevance to this observational study (no CTIMP involved to monitor). Hospitalisations for elective treatment of a pre-existing condition, and hospitalisations as part of routine post-transplant surveillance did not need reporting as SAEs. Unrelated hospitalisations were elicited at the scheduled follow-up appointments and at all emergency appointments.

Serious adverse events requiring expedited reporting included death within 90 days of lung transplantation, severe PGD requiring ECMO/iLA support, bronchial anastomotic dehiscence or any unexpected SAE felt to be probably or definitely causally related to EVLP.

Some SAEs were excluded from expedited reporting to reduce the burden of reporting of events that are common in the transplant journey. These were death on the waiting list prior to transplant or later than 90 days after lung transplantation; PGD grades 1–3 not requiring ECMO/iLA support or 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; and infections requiring an addition or change in antimicrobial therapy.

Medium- and longer-term outcomes that did not require reporting as urgent SAEs were bronchial strictures (whether or not they required bronchial stenting), acute rejection requiring augmented immunosuppression, development of post-transplant lymphoproliferative disease or obliterative bronchiolitis. Finally, deterioration of any pre-existing medical conditions both before and after transplantation did not require urgent reporting.

Public and patient involvement and engagement

The DEVELOP-UK investigators were committed to ensuring appropriate public and patient engagement throughout the study.

The CF Trust was approached to provide patient and service user expertise in the design of the study. Oli Lewington, who has previously undergone lung transplantation, agreed to join the study team in order to help prepare the application for funding, and to contribute to the study design and to the writing of the *Plain English summary*. The chief investigator presented the study proposal to the board of directors of the trust, and the concept of the study to the annual public meeting of the CF Trust. Following award of the funding, Mr Lewington assisted in producing the participant documentation and the final study report.

Lay members were appointed to the Trial Steering Committee to regularly review study progress and to provide valuable public input into key decision-making during the study.

Chapter 3 Main study objectives

Study objectives

The DEVELOP-UK study is the first prospective multicentre study to be performed involving all of the adult cardiopulmonary transplant units across the UK. The objective was to assess the clinical effectiveness and cost-effectiveness of EVLP, a technology allowing objective assessment and reconditioning of unusable donor lungs, in increasing UK lung transplantation activity. Its strategic importance was recognised by the British Transplantation Society, the NHSBT, NHS specialist commissioners and by patient groups during the study design and funding application process.

The DEVELOP-UK study was designed as a non-randomised, non-inferiority observational study with an adaptive design, with two interim analyses planned for when one-third and two-thirds of total enrolment was reached. The planned interim analyses provided the opportunity to determine if the primary end point had been achieved, but also to calculate if any change in sample size was required. The original primary objective was to determine if the 12-month survival of recipients of ex vivo assessed and reconditioned donor lungs (EVLP intervention group) is non-inferior to 12-month survival in recipients of standard donor lungs (control group). The secondary objective was to measure key early clinical outcomes in recipients and changes in their HRQoL in the treatment and control groups in their first post-transplant year. These data were planned to be used in a within-study cost–utility analysis and a Markov model-based evaluation. The former comparison was to be a direct head-to-head comparison of outcomes over 12 months, and the latter was to model the change in availability of lungs as well as extrapolating over the expected lifetime of those needing a lung transplant. In addition, patients' perceptions and understandings of EVLP-reconditioned donor lungs were evaluated in a qualitative substudy.

Timelines and targets

The official start date for the study was 1 January 2012 based on release of NIHR funds to the study team. To allow for local R&D approvals, research staff recruitment and subcontractor contracts with sites to be secured, a 3-month run-in period was proposed, anticipating that recruitment would have started in all sites by 1 April 2012. The actual start date of the study was therefore 1 April 2012. Study recruitment and enrolment was scheduled to run for 36 months, with data collection ending by 42 months, and the final study report was scheduled at 45 months in October 2015. The recruitment targets for the study were set based on official waiting list numbers across the UK in the five adult lung transplant centres. The aim was for a total of 600 patients from the lung transplant waiting list to consent to participate. As this was a non-randomised study, enrolment into the two arms of the study, as defined by undergoing lung transplantation (standard and EVLP transplant), occurred independently, and the study was powered on a predicted 3 : 1 (standard arm to EVLP arm) enrolment ratio. The target for enrolment as lung transplant recipients was 408 patients (306 in standard arm and 102 in EVLP arm).

Trial hypothesis

Had the study run to its planned duration in terms of recruitment, the tested hypothesis was to have been that survival during the first 12 months after transplantation in recipients of EVLP-assessed and -reconditioned donor lungs is non-inferior to that in recipients of standard donor lungs. The primary outcome measure was survival during the first 12 months after lung transplantation.

Consequences for the study analyses of the early closure of the study

The study was powered on survival during the first year post transplant and the target recruitment as 306 patients in the standard transplant arm and 102 in the EVLP transplant arm. This chapter reflects the analysis possible following the early closure of the study, with recruitment of patients stopping in early July 2014 on the advice of the Trial Steering Committee because of a combination of poor recruitment rates into the EVLP arm of the study, and also a safety signal from a higher than expected SAE rate resulting from the need for ECMO support in the EVLP arm. The analyses described below are appropriate to the achieved sample size and differ from that intended and described in the original protocol. The analysis to compare standard with EVLP transplant groups, as well as the analysis of overall survival of patients awaiting transplantation, are descriptive in nature and, as such, do not reflect the initial intention of testing for non-inferiority of EVLP to standard transplants. The originally planned interim analyses, intended to test for the possibility of stoping the study early if non-inferiority was achieved and to re-examine the sample size, did not take place, as the recruitment threshold to trigger the first of these (34 EVLP transplants) was never reached.

Planned timelines for study analysis

In light of the change of circumstances of the analysis, the intent has changed from one of conducting interim analyses to inform the continuation of the study while it was in progress, to one of a single main report of outcome data to the funder. The plan was that data should be available for this analysis from the end of May 2015. In practice, the collection and validation of data were delayed because of the large number of missing data and data queries to sites, meaning that the analysis started in October 2015 and continued into early 2016.

Longer-term analysis plans

It is important to recognise that, despite the early closure of the study, there remains a rich data set, particularly in respect of information on standard transplants and on the total cohort of donor lungs exposed to EVLP. Consideration of this alone was not part of the original comparative analysis plans and, as a result, this is outside the scope of the main study analysis.

Following completion of the main study analyses, and outside the scope of the report to the funder, it will be possible to consider further analysis of the data from the standard transplant arm. This did not form part of the trial statistical analysis plan, as it was not in scope of the originally planned study, but the information from this large contemporary cohort of 200 transplants, including extensive follow-up data, is likely to be useful to future study. Possible approaches include modelling of outcome variables using baseline clinical covariates to identify possible predictors of successful outcome at baseline.

In addition, a comprehensive sampling protocol was in place to collect perfusate, lung tissue and BAL from the donor lungs undergoing EVLP. This will provide a valuable assessment of events at a cellular and molecular level that can be correlated with clinical information within the main study data set. The work on the mechanistic understanding of EVLP falls outside this report (as it is not the subject of the NIHR HTA programme funding), but the tissue sample data will contribute to this subsequent analysis.

Recruitment

The study officially commenced on 1 January 2012, opened to recruitment on 1 April 2012, and closed to recruitment on 9 July 2014. There was a temporary halt in recruitment into the EVLP arm from 6 April 2013 until mid-July 2013, when the study activity in the EVLP arm recommenced with a modified protocol.

The timings for study recruitment in each individual site are shown in *Table 1*. The data analysed and presented in this report were downloaded from the MACRO database in October 2015. Additional data were assembled in Microsoft Excel® 2010 (Microsoft Corporation, Redmond, WA, USA) files for some of the outcome measures (e.g. SF-36 and some lung function measurements) not recorded on CRFs, and for the donor characteristics, which were imported from the NHSBT database.

A total of 593 patients were screened (from records) for eligibility, of whom 98 did not meet eligibility criteria and a further eight declined to participate. Reasons for not meeting the eligibility criteria included age, need for pre-transplant cardiorespiratory support, and listed for heart–lung transplantation or transplantion of lungs and another organ. The screening failure rate was, therefore, only 16.1%, and the refusal rate for participation was just 1.3%.

A total of 487 patients consented to participate or completed an EOI form while on the transplant waiting list, of whom 19 were subsequently removed from the waiting list because of a change in their transplant eligibility, leaving 468 participants eligible to be included in the study. The breakdown of patients consented per participating site is shown in *Table 2*, and the rate at which patient consents were accrued is shown in *Figure 4*.

By the end of the study, 158 participants remained on the waiting list for transplant; 74 had died while waiting, before transplant had occurred, and 34 were excluded after transplant as they did not reconfirm their consent, died before giving consent or were erroneously included after the recruitment cut-off date.

TABLE 1 Approvals and study commencement by site. Dates of NHS R&D approval and first patient consented across five study sites

Site	R&D approval	Delay from 1 January 2012 (official start date)	Date of first EOI/consent	Delay from 1 April 2012 (actual start date)
Newcastle	1 February 2012	1 month	13 April 2012	13 days
Manchester	15 May 2012	5 months 15 days	24 May 2012	1 month 24 days
Cambridge (Papworth)	11 June 2012	6 months 11 days	21 September 2012	6 months 21 days
Birmingham	30 August 2012	8 months	19 September 2012	6 months 19 days
London (Harefield)	9 October 2012	10 months 9 days	26 October 2012	7 months 26 days
Lost recruitment time		31 centre-months		23 centre-months

Note
A centre month is a unit of recruitment time in a multicentre study. 10 centre months might be a single centre recruiting for 10 months or two centres recruiting for 5 months.

TABLE 2 Recruitment (EOI/consent obtained)

Site	Date opened	Number of signed EOI/consent forms
Birmingham	30 August 2012	50
Cambridge (Papworth)	11 June 2012	69
London (Harefield)	9 October 2012	104
Manchester	15 May 2012	84
Newcastle	1 February 2012	180
Total		487

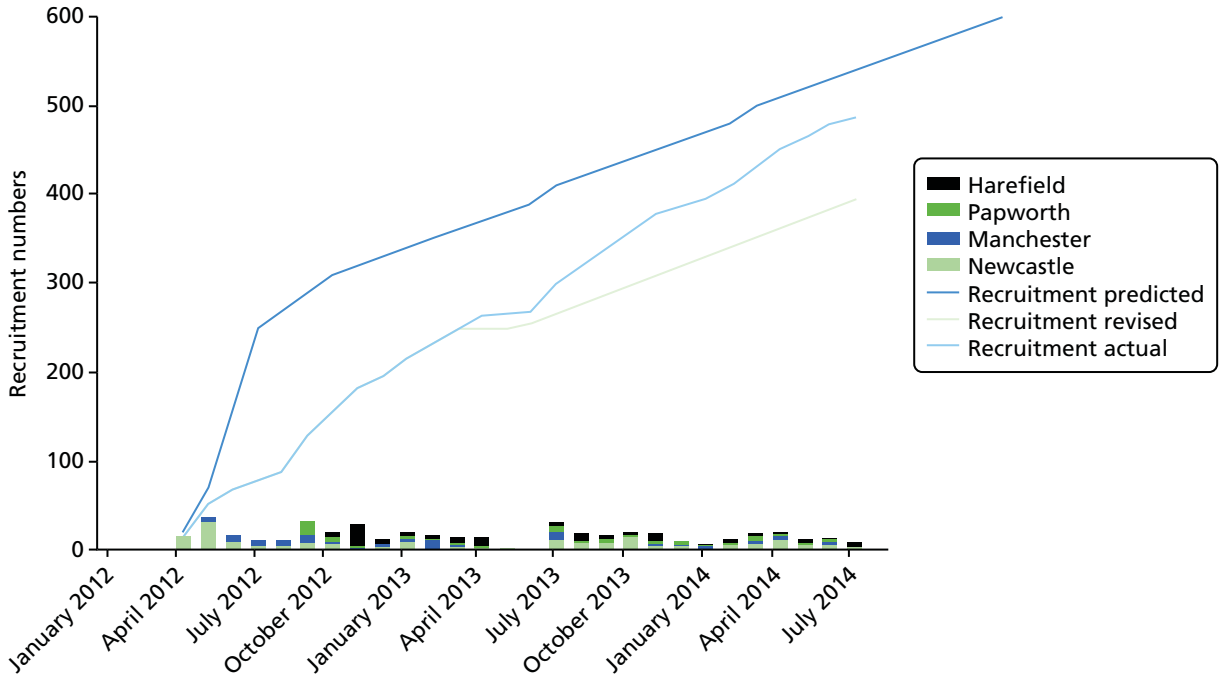

FIGURE 4 Cumulative recruitment numbers across all five centres defined as signing EOI or consent forms.

A total of 202 participants were included in the two transplant arms of the study, 184 in the standard transplant arm [60.1% of the target recruitment of 306, 95% confidence interval (CI) 55.4% to 65.7%] and 18 in the EVLP transplant arm (17.6% of target recruitment of 102, 95% CI 10.8% to 26.4%). A total of 53 EVLP assessments were performed, leading to the 18 transplants, giving a conversion rate of 34.0% (95% CI 26.6% to 42.0%). The transplant activity in the participating sites is shown in *Table 3*. It is the small number in the EVLP transplant arm that drives the need to restrict the comparative analysis to the use of descriptive statistics. A Consolidated Standards of Reporting Trials (CONSORT) diagram showing study activity is shown in *Figure 5*.

The main delay to commencing recruitment to the study resulted from obtaining NHS R&D approvals across the study sites, which equated to 31 centre-months lost.

Two groups of patients were approached: patients already on a transplant waiting list and patients added to the waiting list during the study. As a result, some patients signed an EOI form only, some signed both

TABLE 3 Number of patients transplanted by centre

Centre	Number of transplants (% of total for type)			Number of EVLP assessments (% of total)
	Study group			
	Standard	EVLP	Total	
Birmingham	16 (8.7)	1 (5.6)	17 (8.4)	6 (11.3)
Cambridge (Papworth)	27 (14.7)	2 (11.1)	29 (14.4)	4 (7.5)
London (Harefield)	37 (20.0)	2 (11.1)	39 (19.3)	9 (17.0)
Manchester	22 (12.0)	4 (22.2)	26 (12.9)	7 (13.2)
Newcastle	82 (44.6)	9 (50.0)	91 (45.0)	27 (60.0)
Total	184	18	202	53

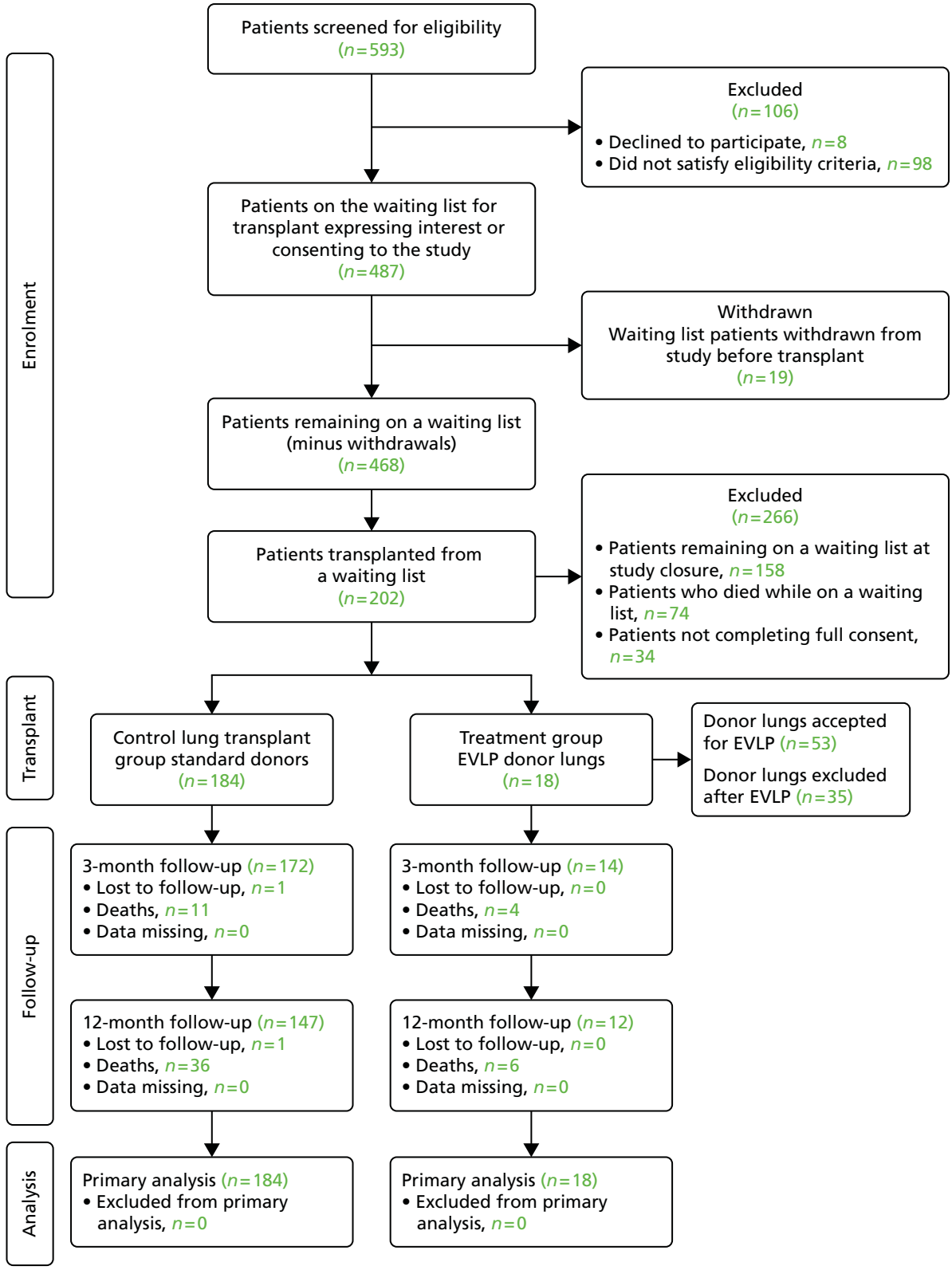

FIGURE 5 The CONSORT diagram: withdrawals.

(an EOI form followed by a consent form during a subsequent routine visit to the transplant centre or on the day of transplant), and some signed only a consent form on the day of transplant, having received study information previously.

No patients requested to be withdrawn from the study after transplantation, and none was withdrawn by study staff on safety grounds. All withdrawals were due to changes in patients' eligibility for lung transplantation or to issues with completion of all necessary consent documents.

Analysis groups

Patients were analysed in groups defined by the type of transplant received [i.e. standard (control) or EVLP (intervention)]. Allocation was not random, and it was not possible to switch between groups. All donors who provided lungs assessed by EVLP ($n = 53$) were included in the descriptive analyses described in *Identifying clinical predictors of successful ex vivo lung perfusion reconditioning*. *Table 4* summarises the times at which the various data were collected for each patient.

Study population

Baseline patient characteristics

There are a number of donor-, recipient- and procedure-related variables that mean that lung transplant recipients constitute a heterogeneous group. The recipient or donor characteristics listed in *Tables 5* and *6* have been identified from the ISHLT registry as those potentially influencing outcomes. *Table 5* summarises characteristics of the lung transplant recipients, split according to the type of transplant. The percentage of recipients who were male and the median age were higher in the EVLP group {72.2% and 56 years [interquartile range (IQR) 46–59 years], respectively} than in the standard transplant group [57.6% and 51 years (IQR 38–58 years), respectively]. About half of the patients in each group had been diagnosed with chronic obstructive pulmonary disease or CF; interstitial lung disease (in the EVLP group) or a combination of interstitial lung disease and emphysema (in the standard group) constituted a further 40% of the diagnoses. The 18 EVLP recipients did possess indicators to suggest that they may have been a higher-risk group, such as significant secondary pulmonary hypertension and requirement for non-invasive ventilation prior to transplant. No lung allocation score is used in the UK and so Lung Allocation Scores or other indicators of clinical urgency were not routinely recorded and cannot be reported.

The percentage of recipients who were diabetic was similar in the EVLP (22.1%) and standard groups (18.1%), as were the median body mass index values, namely 21.6 kg/m^2 (IQR 18.4–26.3 kg/m^2) and 23.8 kg/m^2 (IQR 20.5–26.5 kg/m^2), respectively. The median FEV_1 at baseline was 1.2 l (IQR 0.7–1.9 l) for the EVLP group and 0.9 l (IQR 0.6–1.4 l) for the standard group; the corresponding FEV_1 percentage predicted was 29% (IQR 22–50%) in the EVLP group and 26% (IQR 20–44%) in the standard group. In both groups, > 80% of the lung transplants performed were bilateral. However, the observed percentage of transplants performed with the use of cardiopulmonary bypass was higher in the EVLP group than in the standard group (88.9% vs. 63.0%), although cardiopulmonary bypass status was missing for 12% of patients in the standard group.

The characteristics of the donors, again split between the EVLP and standard transplant groups, are shown in *Table 6*. The percentage of donors who were male was slightly higher in the EVLP group than in the standard group (55.6% vs. 46.7%) and donors in the former group were slightly older (median age 50.5 years and 44 years, respectively). DCD donor type was more common in the EVLP group (27.8% of donors) than in the standard group (16.9%). The numbers of left and right lungs were similar, reflecting – as indicated earlier – the high proportion of transplants that were bilateral. Within each transplant group, ischaemic times were similar for left and right donor lungs. However, total ischaemic times were much higher for EVLP transplants than for standard transplants, which reflects the nature of the procedure.

TABLE 4 Schedule of study activities and data collection points

Study events and data collection	Time on waiting list	Day of transplant	Post-operation ITU stay	Post-operation inpatient stay	1 month (visit 1)	3 months (visit 2)	6 months (visit 3)	12 months (visit 4)
Informed consent or EOI form	✗							
Consent to continue[a]		✗						
Donor data		✗						
Recipient data	✗	✗						
EVLP data (if applicable)		✗						
ITU data/PGD scores		✗	✗					
Chest radiographic data		✗	✗	✗	✗	✗	✗	✗
Blood profile			✗	✗	✗	✗	✗	✗
Length of stay			✗	✗				
Airway healing			✗	✗	✗	✗	✗	
Lung function				✗	✗	✗	✗	✗
Rejection episodes data			✗	✗	✗	✗	✗	✗
Infection episodes data				✗		✗	✗	✗
Hospital admissions data					✗	✗	✗	✗
Use of health services					✗	✗	✗	✗
Patient perceptions (qualitative interviews)	✗						✗	
Quality of life (SF-36)	✗					✗		✗
Survival/cause of death	✗					✗		✗
AEs		✗	✗	✗	✗	✗	✗	✗

a Patients who receive standard lung transplant will not be required to sign the consent to continue form if they have signed the EOI or full informed consent form before the day of transplant.

TABLE 5 Recipient characteristics in the EVLP and standard lung transplant groups

Recipient characteristic	Study group		Total ($N = 202$)
	EVLP ($N = 18$)	Standard ($N = 184$)	
Sex*, n *(%)			
Male	13 (72.2)	106 (57.6)	119 (58.9)
Female	5 (27.8)	78 (42.4)	83 (41.1)
Age (years)			
n	18	183	201
Missing	0	1	1
Median	56	51	52
IQR	46–59	38–58	38–58
Range[a]	20–64	18–70	18–70
Diagnosis*, n *(%)			
COPD	5 (27.8)	40 (21.7)	45 (22.3)
CF	4 (22.2)	47 (25.5)	51 (25.2)
Interstitial lung disease	7 (38.9)	47 (25.5)	54 (26.7)
Emphysema	0 (0)	26 (14.1)	26 (12.8)
Non-CF bronchiectasis	1 (5.6)	8 (4.3)	9 (4.5)
Obliterative bronchiolitis	0 (0)	2 (1.1)	2 (1.0)
Pulmonary hypertension	1 (5.6)	3 (1.6)	4 (2.0)
Other	0 (0)	9 (4.9)	9 (4.5)
Missing	0 (0)	2 (1.1)	2 (1.0)
Diabetes*, n *(%)			
Yes	4 (22.2)	33 (18.1)	37 (18.3)
No	13 (72.2)	142 (78.0)	155 (76.7)
Missing	1 (5.6)	9 (3.9)	10 (5.0)
BMI (kg/m^2)			
n	17	182	199
Missing	1	2	3
Median	21.6	23.8	23.7
IQR	18.4–26.3	20.5–26.5	20.4–26.5
Range[a]	17.6–32.5	15.4–34.2	15.4–34.2
FEV$_1$ (l)			
n	15	176	191
Missing	3	8	11
Median	1.2	0.9	0.9
IQR	0.7–1.9	0.6–1.4	0.6–1.5
Range[a]	0.5–2.5	0.3–3.6	0.3–3.6

TABLE 5 Recipient characteristics in the EVLP and standard lung transplant groups (*continued*)

Recipient characteristic	Study group		Total (*N* = 202)
	EVLP (*N* = 18)	Standard (*N* = 184)	
FEV_1 (%)			
n	15	171	186
Missing	3	13	16
Median	29	26	27
IQR	22–50	20–45	20–45
Range[a]	15–67	11–105	11–105
Type of transplant*, n *(%)			
Single	2 (11.1)[b]	24 (13.0)[c]	26 (13)
Bilateral	16 (88.9)	152 (82.6)	168 (83)
Missing	0 (0)	8 (4.4)	8 (4)
Cardiopulmonary bypass use*, n *(%)			
No	2 (11.1)	46 (25.0)	48 (24)
Yes	16 (88.9)	116 (63.0)	132 (65)
Not known	0 (0)	22 (12.0)	22 (11)

BMI, body mass index; COPD, chronic obstructive pulmonary disease.
a Range: minimum–maximum.
b One left and one right.
c Nine left, 13 right and two not known.

TABLE 6 Donor characteristics

Donor characteristics	Study group		Total (*N* = 202)
	EVLP (*N* = 18)	Standard (*N* = 184)	
Sex*, n *(%)			
Male	10 (55.6)	86 (46.7)	96 (47)
Female	8 (44.4)	96 (52.2)	104 (52)
Missing	0	2 (1.1)	2 (1)
Age			
n	18	181	199
Missing, *n*	0	3	3
Median (years)	50.5	44	46
IQR (years)	47–54	35–54	35–54
Range[a] (years)	22–61	10–68	10–68
Donor type			
n	18	183	201
DBD, *n* (%)	13 (72.2)	152 (82.6)	165 (81)
DCD, *n* (%)	5 (27.8)	31 (16.9)	36 (18)
Missing, *n* (%)	0	1 (0.5)	1 (1)

continued

TABLE 6 Donor characteristics (*continued*)

Donor characteristics	Study group		Total (*N* = 202)
	EVLP (*N* = 18)	Standard (*N* = 184)	
***Side transplanted* (n)**			
Left	17	161	178
Right	17	165	182
Total ischaemic time			
n			
Left	11	136	147
Right	12	141	153
Median (hours)			
Left	12.98	5.8	5.93
Right	13.26	5.45	5.6
IQR (hours)			
Left	10.85–14.35	4.56–6.89	4.65–7.15
Right	10.35–14.49	4.43–6.62	4.5–6.95
Range[a] (hours)			
Left	7.92–19.13	1.12–14.22	1.12–19.13
Right	8.58–17.12	0.82–14.22	0.82–17.12

a Range: minimum–maximum.

Compliance

Seventeen protocol violations were reported in 15 separate patients (7.4% of the total of 202 patients consented and transplanted). Five were major and were due to patients being transplanted with donor lungs that did not fully meet protocol criteria for transplant after EVLP assessment and reconditioning. In all these cases the decision to proceed to transplant was made by the supervising transplant surgeon on the basis of the balance of risks to the patient.

Twelve violations were minor, including approaching patients to give consent for retrospective data collection post standard transplant even though they had not returned an EOI form; failure to obtain full informed consent as the wrong consent form was signed; failure to obtain reconsent to continue on the night of transplant; and, on nine occasions, a > 24-hour delay in the submission of a SAE to the clinical trials unit. Seven of the protocol violations (all minor) were in standard transplant patients, whereas 10 (five major and five minor) were in EVLP transplant patients.

Serious adverse events

There were 42 SAEs affecting 38 patients (16 patients in Newcastle, four patients in London, four patients in Manchester, 11 patients in Cambridge and three patients in Birmingham). Fifteen (35.7%) of these SAEs (affecting 12 patients) occurred in EVLP transplant patients. Details of the SAEs reported are shown in *Table 7*.

Of the 42 SAEs, 18 (42.9%) were a result of death within 90 days of transplant; 14 (77.8% of all fatal SAEs) of these were in standard transplant patients and four (22.2%) were in EVLP patients. Of the total of

TABLE 7 Serious adverse event listing

Participant ID	SAE details (in medical terms, diagnosis if possible)	Seriousness	Outcome	Type of donor organ (standard/EVLP)	Causality	Expectedness
SAE001	Primary diagnosis: interstitial lung disease	Serious	Death	Standard	No causality with inclusion in the study	N/A
SAE002	Readmission to ITU resulting from severe pneumonia. Rising PCO_2 leading to the insertion of a Novalung® (Xenios, Heilbronn, Germany)	Serious, life-threatening	Condition deteriorating	EVLP	No causality with inclusion in the study	N/A
SAE003	Novalung® circuit thrombosed, so device removed	Serious, life-threatening	Death	EVLP	No causality with inclusion in the study	N/A
SAE004	Bilateral lung transplant for Langerhans' cell histiocytosis. Poor oxygenation post-operatively requiring ECMO	Serious, life-threatening	Completely recovered	EVLP	Reasonable possibility that the event may have been caused by inclusion in the study	Expected
SAE005	Multiorgan failure resulting from infection and septicaemia	Life-threatening	Death	Standard	No causality with inclusion in the study	N/A
SAE006	PGD	Serious, life-threatening	Death	Standard	No causality with inclusion in the study	N/A
SAE007	Bilateral lung transplant for CF. Severe hypotension and hypoxia post-cardiopulmonary bypass requiring ECMO	Life-threatening	Condition improving	EVLP	No causality with inclusion in the study	N/A
SAE008	Bilateral lung transplant for CF. Severe hypotension and hypoxia post bypass requiring ECMO support	Life-threatening. Prolonged inpatient hospitalisation	Completely recovered	EVLP	No causality with inclusion in the study	N/A
SAE009	Cardiac arrest resulting from air embolism after patient removed own central line	Life-threatening	Death	EVLP	No causality with inclusion in the study	N/A
SAE010	PGD requiring ECMO as a result of poor oxygenation	Involved or prolonged inpatient hospitalisation	Recovered with sequelae	EVLP	No causality with inclusion in the study	N/A
SAE011	Bleeding right pulmonary artery anastomosis	Not completed	Recovered with sequelae	Standard	No causality with inclusion in the study	N/A
SAE012	PGD requiring ECMO	Life-threatening	Condition improving	Standard	No causality with inclusion in the study	N/A

continued

TABLE 7 Serious adverse event listing (*continued*)

Participant ID	SAE details (in medical terms, diagnosis if possible)	Seriousness	Outcome	Type of donor organ (standard/EVLP)	Causality	Expectedness
SAE013	Persistent air leak due to right main bronchus anastomotic dehiscence. Returned to theatre for refashioning of anastomosis on two occasions. Right pneumonectomy performed	Not completed	Condition improving	Standard	No causality with inclusion in the study	N/A
SAE014	Bilateral lung transplantation for pulmonary fibrosis and emphysema in association with severe PH. Unable to wean from cardiopulmonary bypass; therefore, VA ECMO started	Life-threatening	Condition improving	EVLP	No causality with inclusion in the study	N/A
SAE015	VA ECMO commenced electively in view of patient underlying diagnosis	Not completed	Not completed	Standard	No causality with inclusion in the study	N/A
SAE016	Bilateral pulmonary emboli confirmed on CTPA	Life-threatening, prolonged inpatient hospitalisation	Condition improving	Standard	No causality with inclusion in the study	N/A
SAE017	Death: 1 day post standard lung transplant	Not completed	Death	Standard	No causality with inclusion in the study	N/A
SAE018	Right leg necrotising fasciitis. Caecal volvulus requiring right hemicolectomy	Not completed	Death	Standard	No causality with inclusion in the study	N/A
SAE019	Severe respiratory failure with hypercapnia requiring Novalung® support and retransplantation	Life-threatening, prolonged inpatient hospitalisation	Not completed	Standard	No causality with inclusion in the study	N/A
SAE020	Right pleural cavity infection ± air leak in the right pneumonectomy stump. *Aspergillus* spp. grown in pleural fluid	Not completed	Death	Standard	No causality with inclusion in the study	N/A
SAE021	Left bronchial anastomosis dehiscence	Prolonged inpatient hospitalisation	Condition still present and unchanged	Standard	No causality with inclusion in the study	N/A
SAE022	Multiorgan failure due to *Pseudomonas* spp. Pneumonia	Not completed	Death	Standard	No causality with inclusion in the study	N/A

Participant ID	SAE details (in medical terms, diagnosis if possible)	Seriousness	Outcome	Type of donor organ (standard/EVLP)	Causality	Expectedness
SAE023	Severe RV failure post transplant, commenced ECMO. Returned to theatre and ECMO discontinued	Life-threatening	Condition improving	EVLP	Reasonable possibility that the event may have been caused by inclusion in the study	Expected
SAE024	Commenced on ECMO because of severe graft dysfunction secondary to possible rejection	Not completed	Condition still present and unchanged	Standard	No causality with inclusion in the study	N/A
SAE025	VA ECMO switched to VV ECMO. Continued to deteriorate		Death	Standard	No causality with inclusion in the study	N/A
SAE026	VA ECMO for early PGD	Life-threatening, prolonged inpatient hospitalisation	Condition still present and unchanged	EVLP	Reasonable possibility that the event may have been caused by inclusion in the study	Expected
SAE027	Readmission to ITU because of increasing oxygen requirements	Recovered	Discharged from ITU on 17 December 2013	Standard	No causality with inclusion in the study	N/A
SAE028	Readmitted to ITU because of respiratory failure	Recovered	Not completed	Standard	No causality with inclusion in the study	N/A
SAE029	Readmitted to ITU because of increase in respiratory support requirements	Recovered	Condition improving	EVLP	No causality with inclusion in the study	N/A
SAE030	Patient died due to persistent pneumonia and sepsis < 90 days following transplant after EVLP	Life-threatening	Death	EVLP	No causality with inclusion in the study	N/A
SAE031	Death following chest sepsis and respiratory arrest	Not completed	Death	Standard	No causality with inclusion in the study	N/A
SAE032	Cardiac arrest and severe PGD requiring VV ECMO	Prolonged inpatient hospitalisation	Condition improving	Standard	No causality with inclusion in the study	N/A
SAE033	Severe PGD commenced on ECMO	Life-threatening	Condition still present and unchanged	EVLP	Reasonable possibility that the event may have been caused by inclusion in the study	Expected
SAE034	VV ECMO support started in theatre, now on 30 p.p.m. of nitric oxide	Life-threatening	Condition still present and unchanged	EVLP	Reasonable possibility that the event may have been caused by inclusion in the study	Expected

continued

TABLE 7 Serious adverse event listing (*continued*)

Participant ID	SAE details (in medical terms, diagnosis if possible)	Seriousness	Outcome	Type of donor organ (standard/EVLP)	Causality	Expectedness
SAE035	Right pneumonectomy because of lung necrosis, following bilateral lung transplantation	A prolonged inpatient hospitalisation; persistent or significant disability or incapacity; other significant medical event	Condition improving	Standard	No causality with inclusion in the study	N/A
SAE036	Death within 90 days of transplant; date of death, 3 April 2014	Not completed	Death	Standard	No causality with inclusion in the study	N/A
SAE037	Mortality secondary to respiratory arrest following right lung (EVLP) transplantation	Not completed	Death	EVLP	Reasonable possibility that the event may have been caused by inclusion in the study	Expected
SAE038	ECMO on 23 April 2014 following bilateral lung transplant	Not completed	Condition improving	Standard	No causality with inclusion in the study	N/A
SAE039	Interstitial lung disease; received single lung transplant on 10 June 2014	Not completed	Death	Standard	No causality with inclusion in the study	N/A
SAE040	Gastrointestinal complications. Multiorgan failure. Death	Not completed	Death	Standard	No causality with inclusion in the study	N/A
SAE041	Persistent hypotension, distended abdomen, significant bowel management drainage, decreased white cell count, decreased platelets, heart rate irregular with runs of VT unresponsive to treatment. On CVVH	Not completed	Death	Standard	No causality with inclusion in the study	N/A
SAE042	Bilateral lung transplant for CF. Death within 90 days post transplant	Not completed	Death	Standard	No causality with inclusion in the study	N/A

CTPA, computerised tomography pulmonary angiogram; CVVH, continuous veno-venous haemofiltration; N/A, not applicable; PCO_2, partial pressure of carbon dioxide; PH, pulmonary hypertension; p.p.m., parts per million; RV, right ventricular; VA, veno-arterial; VT, ventricular tachycardia; VV, veno-venous.

42 SAEs, four of these events (9.5%) arising in four patients were judged to be possibly causally related to study procedures; all of these serious adverse reactions were initially considered by the site PI to be possibly unexpected AEs. However, after review by the chief investigator, it was decided that all were in fact events that could be expected to occur after lung transplantation, such as PGD or infection.

Activity in the EVLP arm was halted temporarily on 9 April 2013 for just over 3 months to allow an independent review of the early study outcomes as part of a due diligence process. Before this point, four out of eight transplant recipients in the EVLP arm required ECMO support post-operatively; following resumption of EVLP transplants with a revised protocol, 3 out of 10 transplant recipients required ECMO, but in all cases ECMO duration was limited, all patients were successfully weaned from ECMO, and all except one were successfully discharged from the ITU.

Outcomes analyses

The original intention was that the statistical analysis be conducted in a number of parts: first, a comparison of outcomes between recipients of standard and EVLP transplants to establish non-inferiority; and, second, modelling of the effect of EVLP transplants on the overall survival of patients accepted for lung transplantation in the UK, in order to assess the impact on the service. Furthermore, additional analyses were also to be undertaken to identify clinical predictors with respect to donor characteristics of successful EVLP reconditioning.

The early closure of the study and low numbers in the EVLP arm mean that the analysis methods originally described in the protocol are no longer appropriate. Consequently, the comparative analysis of standard and EVLP transplant groups, as well as the analysis of overall survival of patients awaiting transplantation, reported in *Primary outcome analysis*, are descriptive in nature and, as such, do not reflect the initial intention of testing for non-inferiority of EVLP to standard transplants.

Missing data

From clinical experience of this patient group, it had not been anticipated that there would be significant numbers of dropouts 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 was assessed but, because of the low numbers in the EVLP group, no imputation was performed for any outcome data. However, a significant number of data were missing because they were not collected at the study sites. Most sites worked very hard to keep data collection as complete as possible, but in one site the proportion of missing data was > 20%. The missing data included, but were not limited to, SF-36 questionnaires, detail from outpatient follow-up visits and some information collected during the EVLP procedure.

Primary outcome analysis

Survival in the 12 months following transplantation

The primary outcome of survival in the first 12 months post transplantation was compared in the EVLP and standard transplant groups. *Figure 6* shows the Kaplan–Meier plot of the survival (in days) during the first 12 months post transplantation, split by study group. This analysis takes account of censoring; specifically, one patient (in the standard arm) emigrated during the follow-up, and has been included in the analysis up to the time of the last visit (at 30 days post transplantation).

The numbers of patients who died, survived or were censored during the 12-month follow-up are shown in *Table 8*. The median follow-up was 365 days for both the EVLP and standard transplant groups.

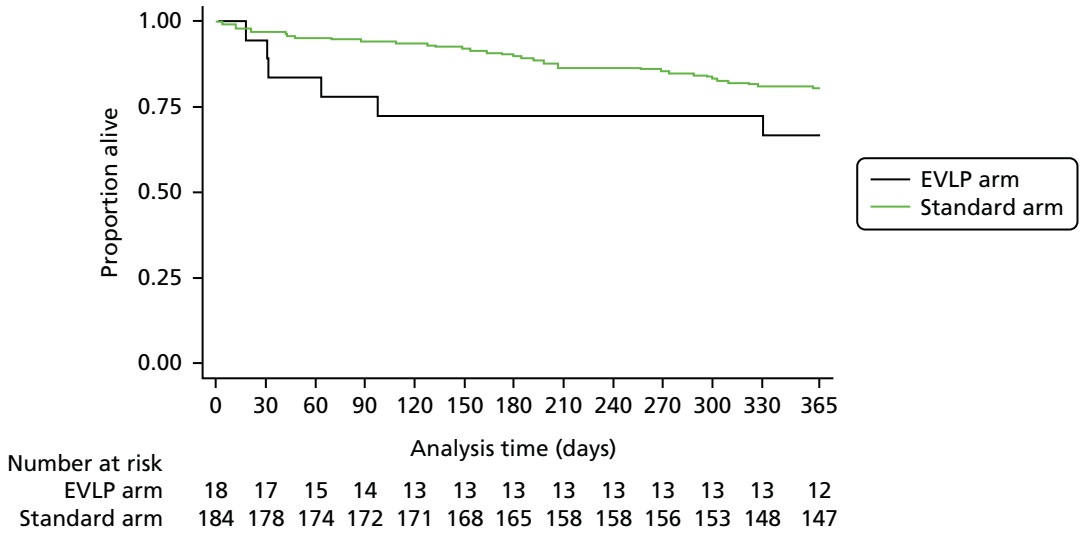

FIGURE 6 Kaplan–Meier survival estimates post transplantation, by study group.

TABLE 8 Numbers of patients who died, survived or were censored during the first 12 months following transplantation

Study group	Died	Survived	Censored	Total
EVLP	6	12	0	18
Hybrid protocol	4	4	0	8
Lund protocol	2	8	0	10
Standard	36	147	1	184
Total of standard and EVLP groups	42	159	1	202

The Kaplan–Meier estimate of survival at 12 months was 0.67 (95% CI 0.40 to 0.83) for the EVLP arm and 0.80 (95% CI 0.74 to 0.85) for the standard arm. Based on Cox regression, the hazard ratio for all-cause mortality in the EVLP arm relative to the standard arm over the 12-month follow-up was 1.96 (95% CI 0.83 to 4.67). This equates to roughly a doubling of the risk of death in the EVLP arm relative to the standard arm, although with a wide CI that encompasses the possibility that mortality might be lower in the EVLP arm than in the standard arm. The width of this CI is influenced greatly by the small number of patients who received an EVLP transplant.

Of the 18 patients who received an EVLP transplant, eight received a transplant based on the hybrid protocol, and 10 received a transplant based on the Lund protocol (see *Table 8*). Survival was then assessed by considering the EVLP protocol groups separately, and *Figure 7* shows the Kaplan–Meier plot of survival separately for patients in the standard, EVLP-Lund and EVLP-hybrid groups.

The Kaplan–Meier estimate of survival at 12 months was 0.80 (95% CI 0.41 to 0.95) for the Lund protocol patients and 0.50 (85% CI 0.15 to 0.77) for the hybrid protocol patients. Based on Cox regression, the hazard ratio for all-cause mortality in the EVLP-hybrid group relative to the EVLP-Lund group over the 12-month follow-up was 2.92 (95% CI 0.53 to 15.95). This wide CI reflects the small numbers of patients in these two EVLP protocol groups.

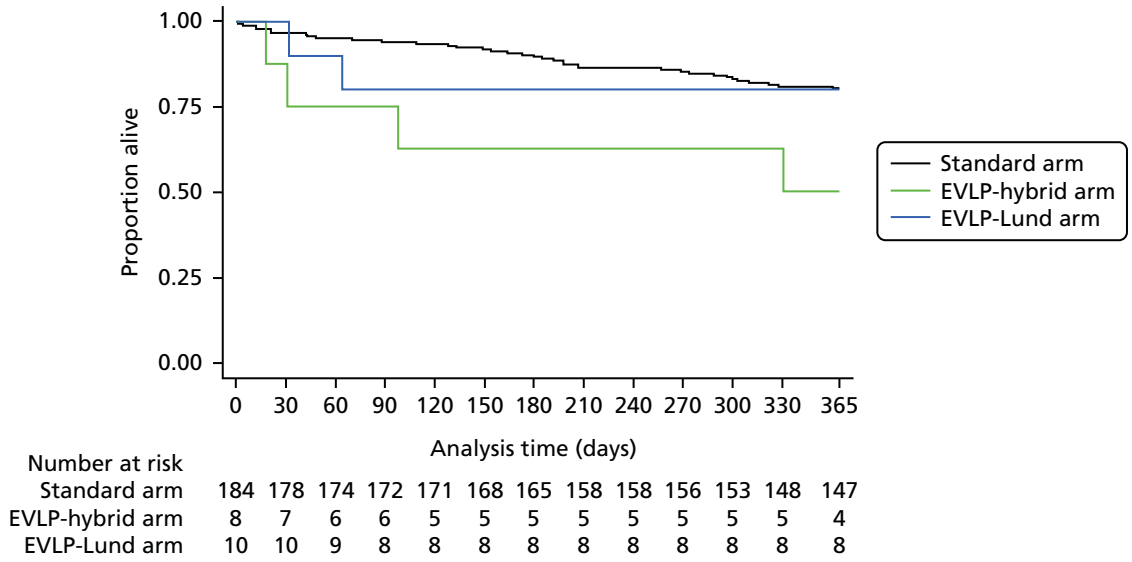

FIGURE 7 Kaplan–Meier survival estimates post transplantation for the standard, EVLP-hybrid and EVLP-Lund study groups.

Secondary outcome measures

Survival at 30 and 90 days

Survival in the early post-operative period after lung transplantation is an important indicator of early complications and is widely used in audit and national and international registries of outcomes. The 30-day survival rates for the EVLP and standard transplant groups are shown in *Table 9* and the 90-day survival rates in *Table 10*.

The Kaplan–Meier estimate of survival at 30 days is 0.94 (95% CI 0.67 to 0.99) for the EVLP arm and 0.97 (95% CI 0.93 to 0.98) for the standard arm. In other words, survival at 30 days was similar for the two transplant groups. The Kaplan–Meier estimate of survival at 90 days was 0.78 (95% CI 0.51 to 0.91) for the EVLP arm and 0.94 (95% CI 0.89 to 0.97) for the standard arm.

TABLE 9 Numbers of patients who died, survived or were censored during the first 30 days following transplantation

Study group	Died	Survived	Censored	Total
EVLP	1	17	0	18
Standard	6	178	0	184
Total	7	195	0	202

TABLE 10 Numbers of patients who died, survived or were censored during the first 90 days following transplantation

Study group	Died	Survived	Censored	Total
EVLP	4	14	0	18
Standard	11	172	1	184
Total	15	186	1	202

Primary graft dysfunction

Primary graft dysfunction is the clinical syndrome of chest radiographic changes and poor oxygenation that represents early acute injury to the transplanted lung. The PGD scores used in the study were as defined in the ISHLT consensus definition.[39] The distribution of the PGD score by study group, measured at baseline and 24, 48 and 72 hours after the transplant, is shown in *Table 11*. A score of 0 represents no evidence of PGD and a score of 3 represents the most severe form of PGD.

The same information, but with the results for grades 0 and 1 combined, is shown in graph format in *Figure 8*. The percentage of patients with PGD grade 3 at baseline was much higher in the EVLP group

TABLE 11 Primary graft dysfunction score by trial arm and time since transplant

	Time point							
	Baseline		24 hours		48 hours		72 hours	
Score	EVLP, *n* (%)	Standard, *n* (%)	EVLP, *n* (%)	Standard, *n* (%)	EVLP, *n* (%)	Standard, *n* (%)	EVLP, *n* (%)	Standard, *n* (%)
Grade 0	1 (5.6)	42 (26.4)	1 (5.6)	43 (27.4)	1 (5.6)	34 (22.5)	1 (5.6)	34 (23.9)
Grade 1	0 (0)	27 (17.0)	3 (16.7)	43 (27.4)	7 (38.9)	51 (33.8)	7 (38.9)	52 (36.6)
Grade 2	1 (5.6)	42 (26.4)	6 (33.3)	43 (27.4)	3 (16.7)	33 (21.9)	5 (27.8)	24 (16.9)
Grade 3	16 (88.9)	48 (30.2)	8 (44.4)	28 (17.8)	7 (38.9)	33 (21.9)	5 (27.8)	32 (22.5)
Total	18	159	18	157	18	151	18	142

Note
Excluding patients with missing data.

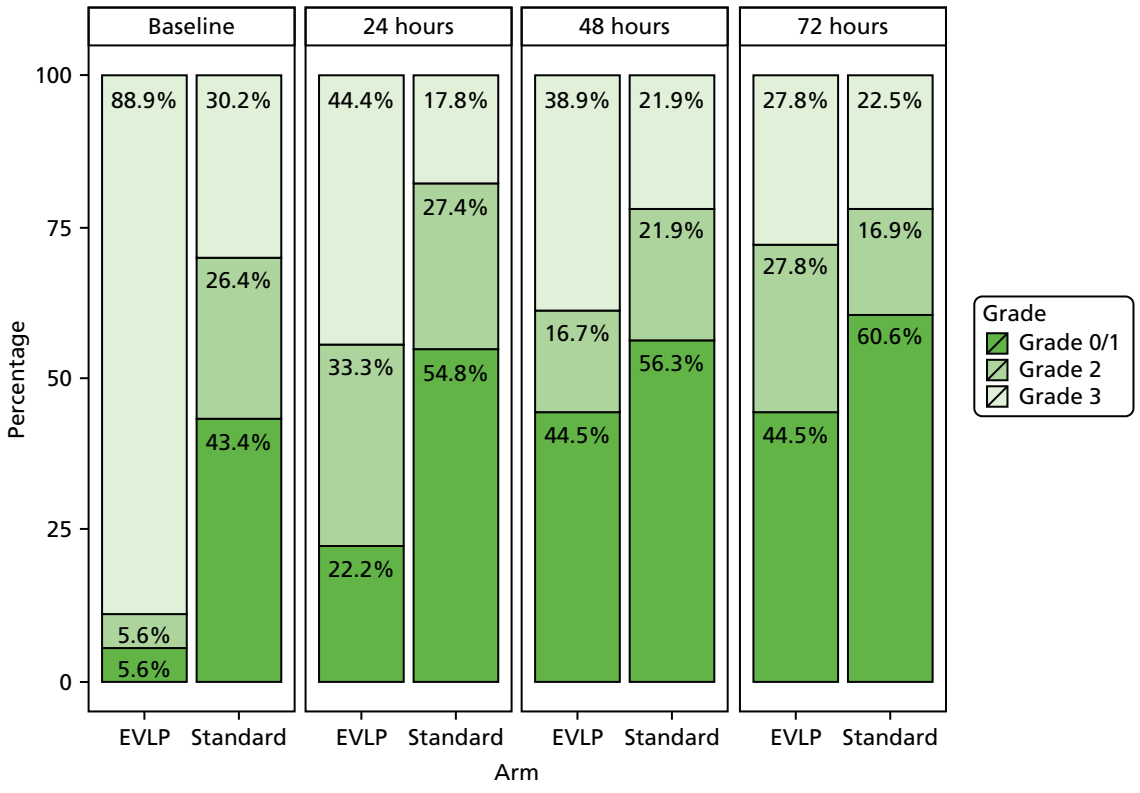

FIGURE 8 Primary graft dysfunction score by trial arm and time since transplant.

than in the standard group (88.9% vs. 30.2%). However, this difference narrowed as time passed, with 27.8% of patients in the EVLP group and 22.5% of those receiving a standard transplant having PGD grade 3 at 72 hours after transplant. Nevertheless, the percentages of patients with grade 0 remained fairly static over time and were higher in the standard group than in the EVLP group (22.5–27.4% and 5.6%, respectively).

Early intensive therapy unit management and duration of hospital stay

Data on several key aspects of the ITU management and hospital stay were collected for all patients transplanted and are presented in *Table 12*. The duration of invasive ventilation tended to be longer for patients receiving an EVLP transplant (median 72 hours, IQR 38–624 hours) than for those receiving a standard transplant (median 38 hours, IQR 19–140 hours). Similarly, ITU stay was longer for EVLP patients (median 14.5 days, IQR 5.4–20.6 days) than for patients with a standard transplant (median 4.3 days, IQR 2.1–10.8 days). However, the overall length of hospital stay was similar for both groups of patients (median of 28 days in both groups) and, among those patients readmitted to ITU, length of stay in ITU was similar in both groups [median 6 days (IQR 3–6 days) in the EVLP arm and 8 days (IQR 3–20.5 days) in the standard arm].

TABLE 12 Summary statistics for duration of invasive ventilation, ITU stay, hospital stay before first discharge in days and (where relevant) ITU readmission

	Study group		
ITU management and hospital stay	EVLP ($N = 18$)	Standard ($N = 184$)	Total ($N = 202$)
Invasive ventilation			
n	18	174	192
Median (hours)	72	38	43
IQR (hours)	38–624	19–140	20–180.5
Range[a] (hours)	8–2400	0–2208	0–2400
ITU stay			
n	18	160	178
Median (days)	14.5	4.3	4.8
IQR (days)	5.4–20.6	2.1–10.8	2.6–15
Range[a] (days)	1.7–98	0.4–100.6	0.4–100.6
Hospital stay			
n	18	163	181
Median (days)	28	28	28
IQR (days)	21–46	18–43	18–44
Range[a] (days)	16–100	2–99	2–100
ITU readmission			
n	3	28	31
Median (days)	6	8	6
IQR (days)	3–6	3–20.5	3–18
Range[a] (days)	3–6	1–80	1–80

a Range: minimum–maximum.

Post-operative infection

The number of patients with at least one post-operative infection, both at baseline and during subsequent follow-up periods, is shown in *Table 13*. The associated percentages are displayed graphically in *Figure 9*. At baseline, just under half of patients in both the EVLP group and the standard group had at least one post-operative infection. In both groups, the percentage of patients with at least one post-operative infection dropped subsequently, as shown in *Figure 6*. This percentage tended to be lower in the EVLP

TABLE 13 Numbers of patients with at least one post-operative infection, at baseline and during subsequent periods

	Time period									
	Baseline, *n* (%)		Baseline–1 month, *n* (%)		1–3 months, *n* (%)		3–6 months, *n* (%)		6–12 months, *n* (%)	
Category	EVLP	Standard	EVLP	Standard	EVLP	Standard	EVLP	Standard	EVLP	Standard
Number of patients with at least one episode	7 (46.7)	81 (45.5)	2 (15.4)	37 (23.9)	2 (15.4)	38 (21.5)	3 (23.1)	38 (24.5)	2 (18.2)	39 (29.1)
Number at risk	18	184	18	184	17	178	14	172	13	165

Notes
Percentages are given relative to the total.
The number at risk is based on those at risk at the start of the relevant period.

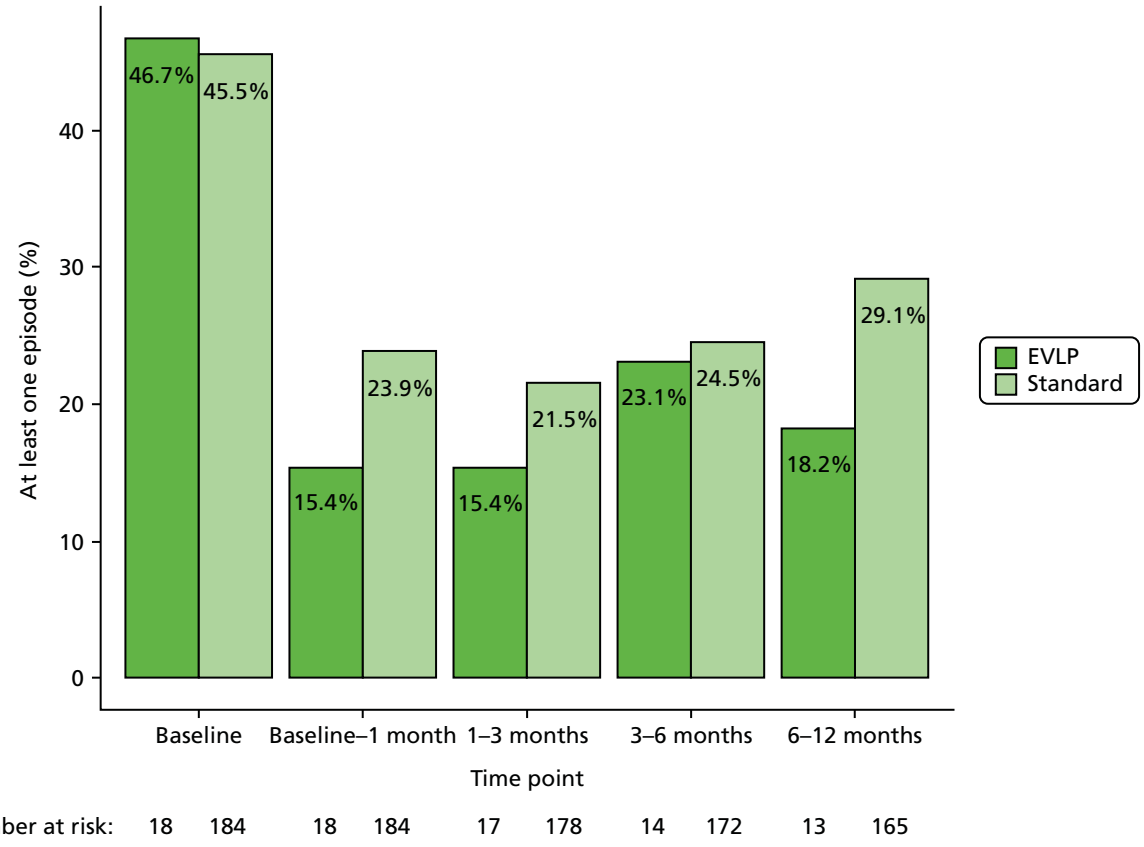

FIGURE 9 Percentage of patients with at least one post-operative infection, at baseline and during subsequent periods, by study group. Note that the number at risk is based on those at risk at the start of the relevant period.

group than in the standard group. However, inferences are limited by the small numbers of patients with infections in the EVLP group.

The number of episodes and number of organisms involved in specific post-operative infections are detailed in *Table 14*. The most common organisms involved were *Pseudomonas*, *Staphylococcus*, *Escherichia coli* and *Candida* species. Owing to small numbers, it is difficult to compare any differences in the spectra of infections in the EVLP and standard groups.

TABLE 14 Numbers of episodes and organisms involved in specific post-operative infections, at baseline and during subsequent follow-up periods

	Time period									
	Baseline, *n* (%)		Baseline–1 month, *n* (%)		1–3 months, *n* (%)		3–6 months, *n* (%)		6–12 months, *n* (%)	
Organism	EVLP	Standard	EVLP	Standard	EVLP	Standard	EVLP	Standard	EVLP	Standard
Pseudomonas	5 (29.4)	19 (12.8)	1 (33.3)	6 (15.0)	1 (50.0)	4 (7.7)	0 (0)	5 (12.2)	0 (0)	5 (11.1)
Staphylococcus	4 (23.5)	27 (18.1)	0 (0)	6 (15.0)	0 (0)	3 (5.8)	0 (0)	2 (4.9)	0 (0)	2 (4.4)
Coliforms	0 (0)	7 (4.7)	0 (0)	1 (2.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Escherichia coli	1 (5.9)	11 (7.4)	1 (33.3)	0 (0)	0 (0)	1 (1.9)	0 (0)	1 (2.4)	0 (0)	1 (2.2)
Clostridium difficile	0 (0)	4 (2.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Klebsiella	0 (0)	5 (3.4)	0 (0)	1 (2.5)	0 (0)	1 (1.9)	2 (50.0)	2 (4.9)	0 (0)	1 (2.2)
Haemophilus	1 (5.9)	5 (3.4)	0 (0)	1 (2.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Aspergillus	0 (0)	5 (3.4)	0 (0)	2 (5.0)	0 (0)	3 (5.8)	0 (0)	2 (4.9)	1 (25.0)	5 (11.1)
Candida	1 (5.9)	14 (9.4)	0 (0)	2 (5.0)	0 (0)	3 (5.8)	0 (0)	0 (0)	0 (0)	1 (2.2)
Influenza virus	1 (5.9)	1 (0.7)	0 (0)	1 (2.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4.4)
Adenovirus	0 (0)	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Rhinovirus	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (5.8)	0 (0)	0 (0)	1 (25.0)	0 (0)
Herpesvirus	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.4)	0 (0)	3 (6.7)
Streptococcus	0 (0)	2 (1.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Mycobacterium	0 (0)	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Scedosporium	0 (0)	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Stenotrophomonas	1 (5.9)	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4.4)
Other specified	3 (17.6)	34 (22.8)	1 (33.3)	12 (30.0)	0 (0)	21 (40.4)	1 (25.0)	14 (34.1)	1 (25.0)	10 (22.2)
Organism not specified	0 (0)	11 (7.4)	0 (0)	8 (20.0)	1 (50.0)	13 (25.0)	1 (25.0)	14 (34.1)	1 (25.0)	13 (28.9)
Total number of organisms	17	149	3	40	2	52	4	41	4	45
Total number of episodes	16	144	3	38	2	52	4	41	4	44

Notes
Percentages are given relative to the total number of organisms. Each episode may have involved more than one organism. Patients may have had more than one episode. Anastomotic complications.

It is recognised that ischaemic injury to the donor lung could adversely affect the bronchus and lead to bronchial complications. It was therefore important to consider if there was any difference in rates of anastomotic complications between the study groups. In *Table 15*, the numbers of patients with anastomotic complications are presented by study group and time since transplant. None of the patients in the EVLP group had such complications at any of the follow-up times. In the standard group, the percentage of patients with these complications varied between 4.4% and 9.6% over the follow-up period.

The Couraud Classification of anastomotic healing provides a means to quantify the degree of healing that may be an indicator of low-level ischaemic injury.[40] These scores are presented numerically by study group and time since transplant in *Table 16*, and as percentages in graphical format in *Figure 10*. Among both EVLP and standard transplant patients, the percentage with grade 1 healing tended to increase over the period of the follow-up, from around 40% between baseline and 1 month to just over 80% between 6 and 12 months. Over the same period, the percentage of patients with grade 2 healing decreased, from around 50% between baseline and 1 month to roughly 16% between 6 and 12 months.

TABLE 15 Numbers of patients with anastomotic complications, by study group and time since transplant

	Time period							
	Baseline–1 month, *n* (%)		1–3 months, *n* (%)		3–6 months, *n* (%)		6–12 months, *n* (%)	
Category	EVLP	Standard	EVLP	Standard	EVLP	Standard	EVLP	Standard
Number of patients with anastomotic complications	0 (0)	12 (6.7)	0 (0)	7 (4.4)	0 (0)	12 (8.0)	0 (0)	14 (9.6)
Total	18	179	14	160	13	150	12	146
Number at risk	18	184	17	178	14	172	13	165

Note
Percentages are given relative to the total.

TABLE 16 Anastomotic healing among patients (based on the Couraud Classification), by study group and time since transplant

	Time period							
	Baseline–1 month, *n* (%)		1–3 months, *n* (%)		3–6 months, *n* (%)		6–12 months, *n* (%)	
Score	EVLP	Standard	EVLP	Standard	EVLP	Standard	EVLP	Standard
Grade 1	4 (36.4)	38 (41.3)	2 (25.0)	51 (47.2)	6 (85.7)	68 (68.7)	5 (83.3)	67 (82.7)
Grade 2A	5 (45.5)	30 (32.6)	6 (75.0)	39 (36.1)	1 (14.3)	24 (24.2)	1 (16.7)	12 (14.8)
Grade 2B	1 (9.1)	17 (18.5)	0 (0)	13 (12.0)	0 (0)	2 (2.0)	0 (0)	1 (1.2)
Grade 3A	1 (9.1)	4 (4.3)	0 (0)	4 (3.7)	0 (0)	5 (5.1)	0 (0)	1 (1.2)
Grade 3B	0 (0)	3 (3.3)	0 (0)	1 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)
Total	11	92	8	108	7	99	6	81
Number at risk	18	184	17	178	14	172	13	165

Note
Percentages are given relative to the total.

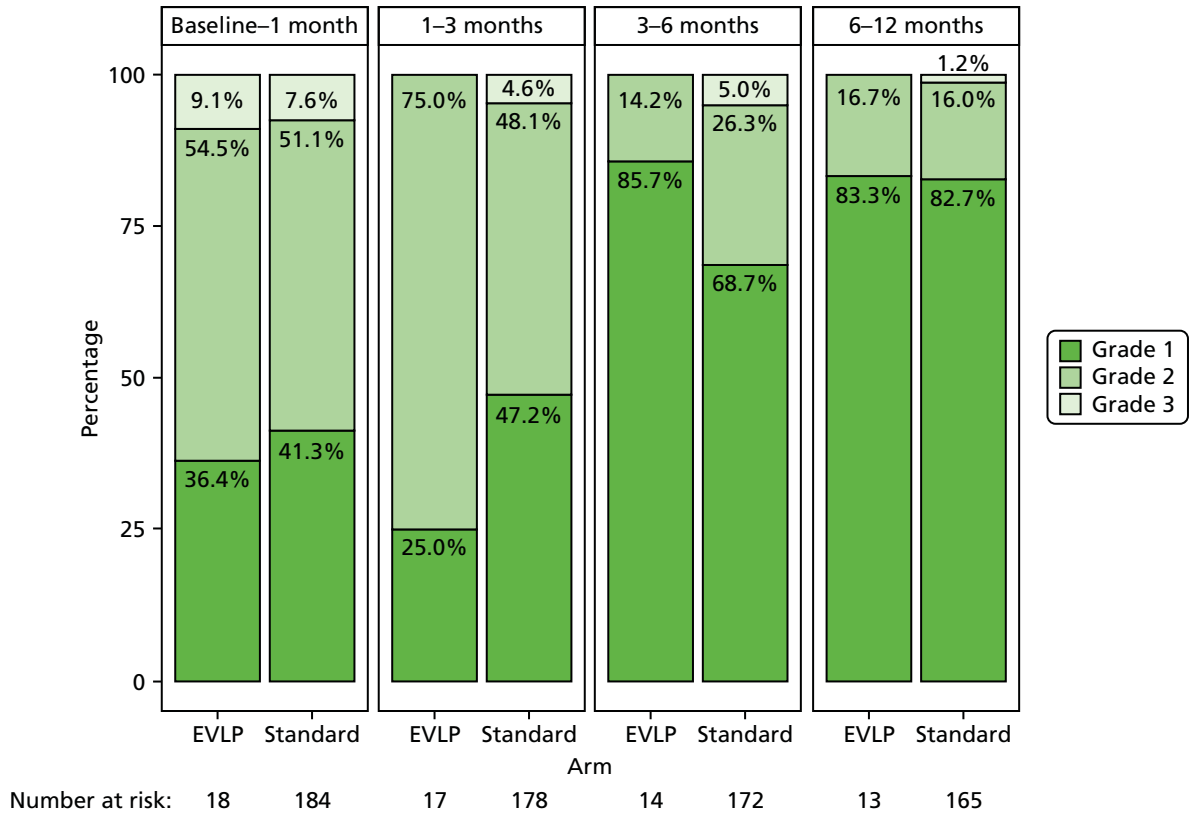

FIGURE 10 Anastomotic healing among patients (based on the Couraud Classification), by study group and time since transplant.

Lung function measurements

Measurement of FEV_1 in both absolute volume in litres and as a percentage of the patient's predicted values based on age, sex, height and measurement of forced vital capacity (FVC) in litres is routinely performed as part of post-lung transplant follow-up. This information is presented in *Table 17* and also displayed in box plots in *Figures 11–13*. Each of these measures tended to increase with increasing length of follow-up. In addition, median values for the EVLP and standard transplant groups were generally similar.

Abnormalities on chest radiographs

The number of patients with abnormalities on chest radiographs, both at baseline and at subsequent follow-up visits over the 12 months after transplant, is shown in *Table 18*. The associated percentages are also displayed graphically in *Figure 14*. These percentages were lower at 6 and 12 months than at earlier times. There is also some suggestion that abnormalities were slightly less common in the EVLP group than in the standard group, although inferences are limited because of the small numbers of EVLP patients with abnormalities.

The nature of the specific abnormalities on chest radiographs is shown in *Table 19*. Overall, effusion was the most common abnormality, followed by pneumothorax, consolidation, atelectasis and shadowing. Owing to the small numbers in EVLP group, it is not possible to compare the spectra of abnormalities between the EVLP and standard groups.

The number of episodes of allograft alloimmune injury was collected in both study groups. Data on acute vascular rejection by ISHLT score, presence of antibody-mediated rejection and lymphocytic bronchiolitis are presented in *Table 20* as numbers of rejection episodes by rejection type, study group and time period. Overall, these episodes were less frequent > 3 months after transplant than at earlier times. This decrease was particularly notable for A2+ episodes. The percentage of patients with at least one rejection episode was generally similar for the EVLP and standard groups.

TABLE 17 Lung function measurements by study group and time since transplant

Lung function parameter	Time point							
	1 month		3 months		6 months		12 months	
	EVLP	Standard	EVLP	Standard	EVLP	Standard	EVLP	Standard
Number at risk	17	178	14	172	13	165	12	147
FEV_1								
n[a]	10	124	13	150	13	149	11	129
Median (l)	2.26	2.07	2.26	2.29	2.53	2.38	2.82	2.44
IQR (l)	1.87–3.15	1.68–2.60	1.89–2.68	1.79–2.70	2.23–3.65	1.85–2.83	2.12–3.37	1.95–2.93
Range[b] (l)	1.54–3.89	0.77–3.85	1.17–4.46	0.80–4.53	1.53–4.83	0.74–4.75	1.88–4.30	0.78–4.90
FEV_1								
n[a]	9	111	12	138	13	129	9	116
Median (% predicted)	58	69	71	71	85	78	93	77.5
IQR (% predicted)	45–74	55–81	51–84	57–87	65–106	63–91	62–97	65.5–91.5
Range[b] (% predicted)	44–97	25–100	34–131	29–135	44–142	23–143	51–99	30–143
FVC								
n[a]	10	123	13	150	12	149	11	128
Median (l)	2.70	2.49	2.80	2.70	3.23	3.03	3.35	3.53
IQR (l)	2.60–3.15	1.91–3.08	2.48–3.71	2.25–3.27	2.67–4.28	2.41–3.60	2.66–3.89	2.75–4.34
Range[b] (l)	1.90–4.10	1.16–4.80	1.82–4.53	0.92–5.35	1.82–5.88	0.85–5.84	1.98–5.56	1.14–5.96

a Number from which data are available.
b Range: minimum–maximum.

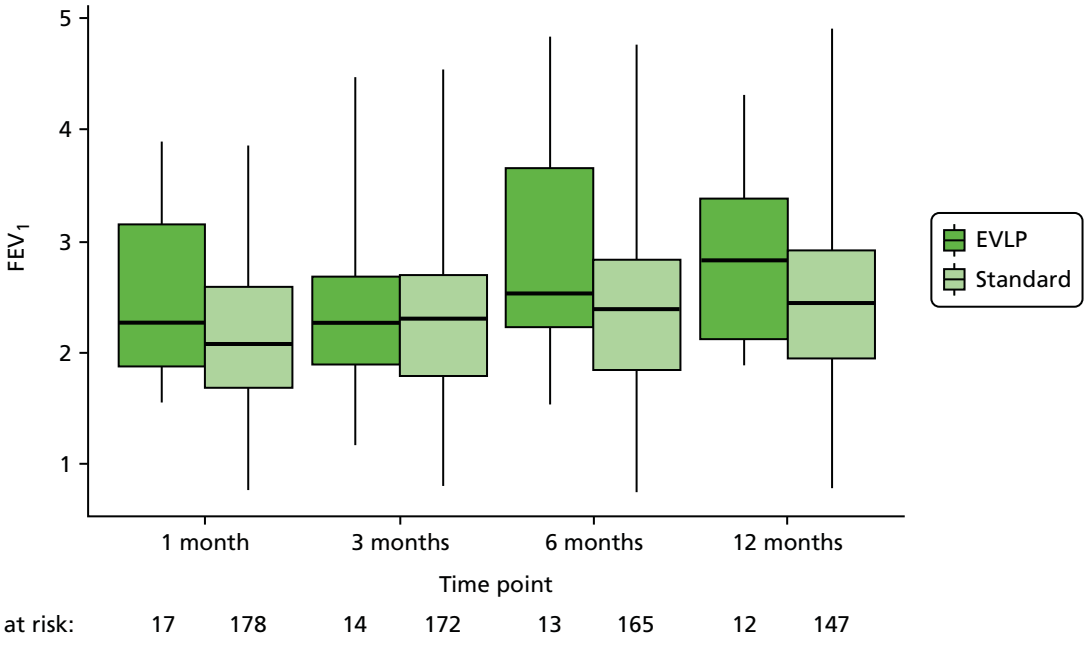

FIGURE 11 Box plot of FEV_1 by time since transplant.

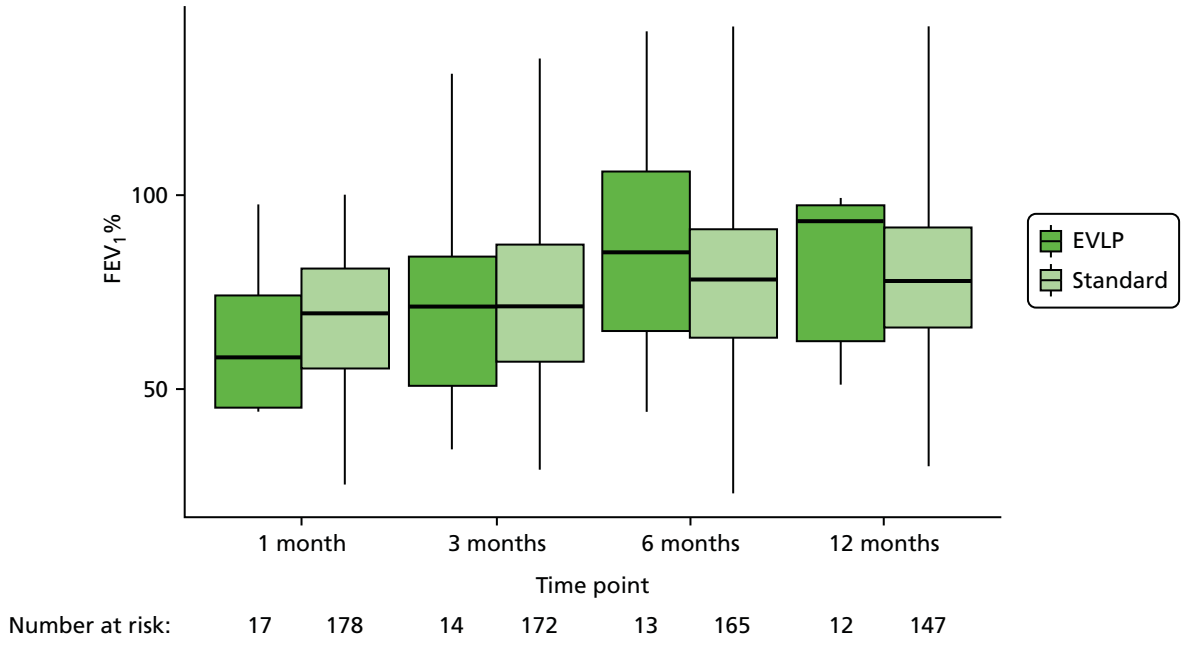

FIGURE 12 Box plot of FEV_1% by time since transplant.

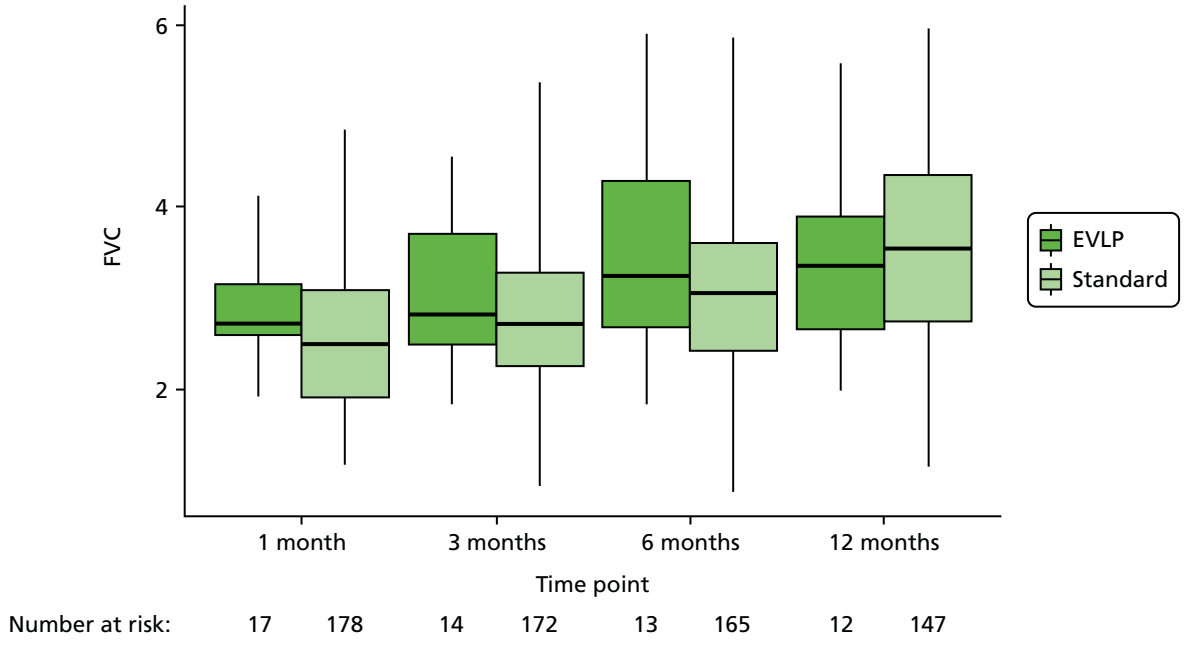

FIGURE 13 Box plot of FVC by time since transplant.

Short Form questionnaire-36 items health-related quality-of-life measure

The assessment of HRQoL in the DEVELOP-UK study was done using a well-validated questionnaire, the SF-36. The SF-36 is a measure of general health that generates eight dimensions and two summary scores from 36 different questions.[46] In order to do so, each one of the 36 questions of the survey relates to a different pre-coded numeric value. In order to interpret the SF-36 data, the raw scores should be translated into a value from 0 (lowest or worst possible level of HRQoL) to 100 (highest or best possible level of HRQoL). These translated scores are then used to calculate the mean for each one of the following eight domains: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems and general mental health. From these eight concepts, two summary measures of norm-based mental component score (MCS)

TABLE 18 Numbers of patients with abnormalities on chest radiographs, by study group and time since transplant

	Time point									
	Baseline, *n* (%)		1 month, *n* (%)		3 months, *n* (%)		6 months, *n* (%)		12 months, *n* (%)	
Category	EVLP	Standard	EVLP	Standard	EVLP	Standard	EVLP	Standard	EVLP	Standard
Number of patients with abnormality on chest radiographs	7 (46.7)	105 (61.8)	7 (53.8)	96 (60.0)	7 (58.3)	66 (42.9)	2 (18.2)	48 (33.3)	2 (22.2)	28 (24.6)
Total	15	170	13	160	12	154	11	144	9	114
Number at risk	18	184	17	178	14	172	13	165	12	147

Note
Percentages are given relative to the total.

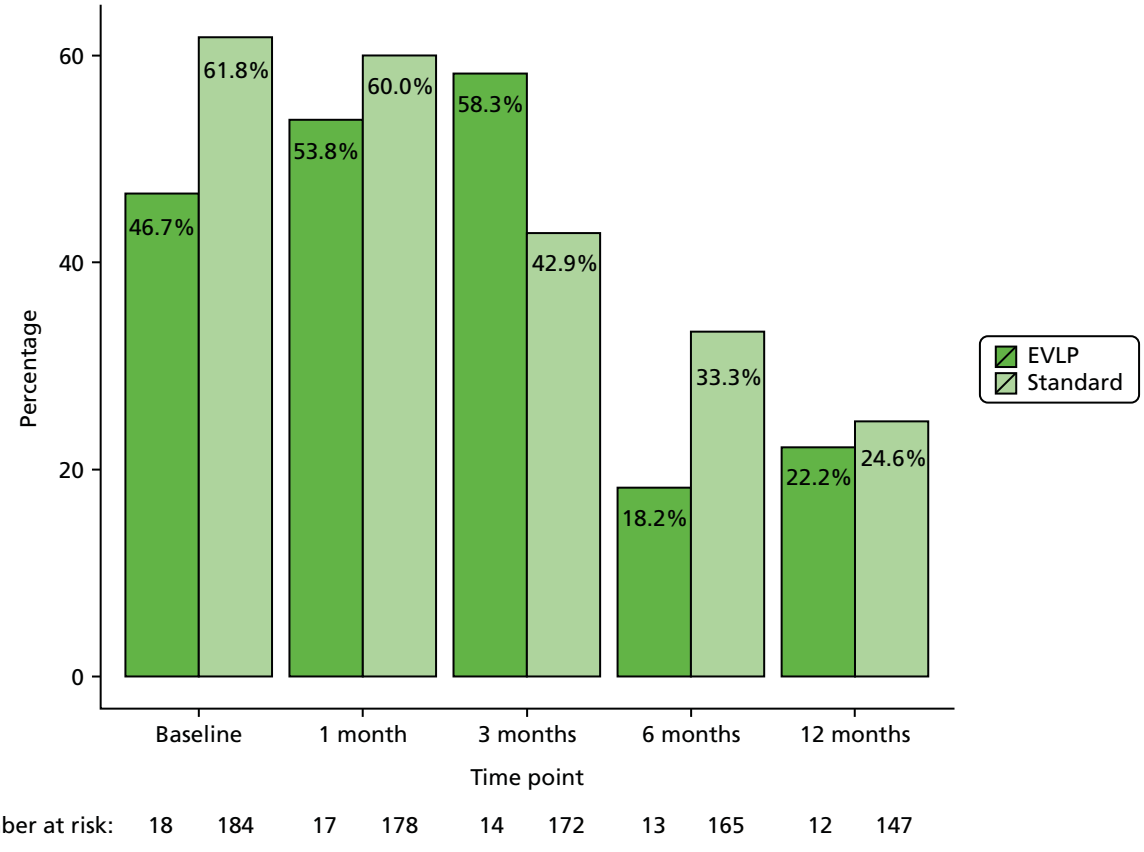

FIGURE 14 Percentage of patients with abnormalities on chest radiographs, by study group and time since transplant.

and physical component score (PCS), with a mean of 50 and a standard deviation (SD) of 10 in a general population, can be constructed from all the emotionally and physically relevant items, respectively.[47] The higher the value of the summary scores the higher the level of functionality of the patient.

Short Form questionnaire-36 items data analysis

The SF-36 questionnaires were completed while the recipients were still on the waiting list, as well as at 3 and 12 months post transplant, and their mean scores were converted into health-state utilities using the

TABLE 19 Numbers of specific abnormalities on chest radiographs, by study group and time since transplant

Type of abnormality	Time point									
	Baseline, *n* (%)		1 month, *n* (%)		3 months, *n* (%)		6 months, *n* (%)		12 months, *n* (%)	
	EVLP	Standard	EVLP	Standard	EVLP	Standard	EVLP	Standard	EVLP	Standard
Pneumothorax	0 (0)	21 (15.9)	1 (8.3)	12 (9.3)	0 (0)	6 (9.0)	0 (0)	3 (6.7)	0 (0)	2 (6.9)
Effusion	3 (37.5)	55 (41.7)	4 (33.3)	57 (44.2)	4 (50.0)	29 (43.3)	1 (100.0)	15 (33.3)	1 (50.0)	7 (24.1)
Consolidation	3 (37.5)	20 (15.2)	3 (25.0)	22 (17.1)	0 (0)	3 (4.5)	0 (0)	4 (8.9)	0 (0)	3 (10.3)
Atelectasis	1 (12.5)	16 (12.1)	2 (16.7)	17 (13.2)	3 (37.5)	9 (13.4)	0 (0)	8 (17.8)	1 (50.0)	7 (24.1)
Collection	0 (0)	5 (3.8)	1 (8.3)	4 (3.1)	0 (0)	2 (3.0)	0 (0)	0 (0)	0 (0)	0 (0)
Shadowing	0 (0)	13 (9.8)	1 (8.3)	16 (12.4)	1 (12.5)	12 (17.9)	0 (0)	11 (24.4)	0 (0)	5 (17.2)
Elevated hemidiaphragm	1 (12.5)	0 (0)	0 (0)	0 (0)	0 (0)	4 (6.0)	0 (0)	3 (6.7)	0 (0)	1 (3.4)
No valid description	0 (0)	2 (1.5)	0 (0)	1 (0.8)	0 (0)	2 (3.0)	0 (0)	1 (2.2)	0 (0)	4 (13.8)
Total number of abnormalities	8	132	12	129	8	67	1	45	2	29

Notes
Percentages are expressed relative to the total number of abnormalities.
Acute rejection and associated alloimmune injury.

TABLE 20 Number of rejection episodes by rejection type, study group and time period

Category	Time period							
	Baseline–1 month, *n* (%)		1–3 months, *n* (%)		3–6 months, *n* (%)		6–12 months, *n* (%)	
	EVLP	Standard	EVLP	Standard	EVLP	Standard	EVLP	Standard
A1	0 (0)	11 (22.9)	1 (16.7)	13 (26.5)	0 (0)	5 (19.2)	0 (0)	12 (57.1)
A2+	4 (100.0)	30 (62.5)	4 (66.7)	25 (51.0)	1 (50.0)	11 (42.3)	1 (50.0)	8 (38.1)
Antibody-mediated rejection	0 (0)	0 (0)	0 (0)	1 (2.0)	0 (0)	0 (0)	0 (0)	0 (0)
Clinical rejection without biopsy	0 (0)	1 (2.1)	0 (0)	2 (4.1)	0 (0)	0 (0)	0 (0)	0 (0)
Lymphocytic bronchiolitis	0 (0)	1 (2.1)	0 (0)	2 (4.1)	0 (0)	1 (3.8)	0 (0)	0 (0)
Not classified	0 (0)	5 (10.4)	1 (16.7)	6 (12.2)	1 (50.0)	9 (34.6)	1 (50.0)	1 (4.8)
Total number of episodes	4	48	6	49	2	26	2	21
Number of patients with at least one rejection episode[a]	4 (22.2)	48 (26.1)	6 (35.3)	46 (27.0)	2 (14.3)	26 (15.1)	2 (15.4)	20 (12.1)
Number of patients at risk[b]	18	184	17	178	14	172	13	165

a The percentage of patients with at least one rejection episode is given relative to the number of patients at risk.
b Based on those at risk at the start of the period.
Note
Precentages are expressed relative to the total number of episodes.

SF-6D algorithm[48] described in *Chapter 4*. In the SF-36 data analysis, the mean (SD) and median (IQR) score for each of the eight domain scores were estimated for each one of the two study groups and for each time point. The SF-36 data were also used to estimate the mean, SD, median and IQR for MCS and PCS scores by study group. No hypothesis testing or modelling was undertaken and no imputation was performed other than that which forms part of the standard scoring system for the SF-36.

The SF-36 data, available at each time point of the study, as well as the number of participants with missing data for both the standard and EVLP trial arms, are summarised in *Table 21*. A significant number of participants did not complete the SF-36 at each of the three time points identified in the study protocol. The absolute number of patients for whom SF-36 data were collected at different stages of the study is shown in *Table 22*.

The detailed scores of the SF-36 questionnaires are presented in *Tables 23* and *24*. The mean, SD, median, IQR and range of the eight domain scores and the two summary scores, respectively, at each data collection point for each of the two transplant procedures are presented. These two tables also report the number of responses at each time point, together with the number of patients at risk (i.e. the number that would have been eligible to complete the SF-36).

TABLE 21 Number of SF-36 measurements at each time point of the study and by study group

	Study group		
Time point	EVLP, *n* (%)[a]	Standard, *n* (%)	Total, *n* (%)
Waiting list	8 (38.1)	67 (40.1)	75 (39.9)
3 months post transplant	7 (33.3)	52 (31.1)	59 (31.4)
12 months post transplant	6 (28.6)	48 (28.7)	54 (28.7)
Total number of measurements	21	167	188
Number of patients with no SF-36 data	6	83	89

a To aid interpretation, six participants in the EVLP arm did not complete the SF-36 at any data collection time points and eight completed the questionnaire while on the waiting list.

TABLE 22 Numbers of patients with SF-36 data available for each stage of the study

	Time point						
Category	Baseline	3 months	12 months	Baseline and 3 months	Baseline and 12 months	3 and 12 months	Baseline, 3 and 12 months
EVLP							
Number of patients (%)[a]	8 (44.4)	7 (50.0)	6 (50.0)	4 (28.6)	2 (16.7)	4 (33.3)	1 (8.3)
Number at risk	18	14	12	14	12	12	12
Standard							
Number of patients (%)	67 (36.4)	52 (30.2)	48 (32.7)	31 (18.0)	27 (18.4)	26 (17.7)	18 (12.2)
Number at risk	184	172	147	172	147	147	147
Total							
Number of patients (%)	75 (37.1)	59 (31.7)	54 (34.0)	35 (18.8)	29 (18.2)	30 (18.9)	19 (11.9)
Number at risk	202	186	159	186	159	159	159

a Percentages are given relative to the number of patients at risk at the latest of the times considered.

TABLE 23 Short Form questionnaire-36 items domain scores at each data collection point of the study, by study group

Domain	Study group					
	Standard			EVLP		
	Baseline ($n = 67$)	3 months ($n = 52$)	12 months ($n = 48$)	Baseline ($n = 8$)	3 months ($n = 7$)	12 months ($n = 6$)
Number at risk	184	172	147	18	14	12
Bodily pain						
Median (IQR)	46.68 (38.21–55.55)	49.10 (40.63–55.55)	55.55 (46.68–62.00)	53.53 (46.68–62.00)	51.51 (51.51–62.00)	62.00 (55.55–62.00)
95% CI	42.61 to 48.36	45.35 to 51.00	48.55 to 54.85	43.02 to 61.22	42.29 to 61.89	56.36 to 63.35
General health						
Median (IQR)	23.71 (21.33–30.84)	48.43 (38.92–55.56)	48.43 (42.02–55.56)	28.46 (22.52–29.65)	57.94 (50.81–62.70)	55.56 (54.61–55.56)
95% CI	24.41 to 28.25	43.87 to 49.67	45.19 to 51.28	22.95 to 32.19	52.62 to 62.60	50.53 to 62.02
General mental health						
Median (IQR)	45.64 (37.79–53.48)	53.48 (44.33–58.72)	53.48 (45.64–58.72)	44.33 (41.71–49.56)	58.72 (53.48–61.33)	60.03 (53.48–63.95)
95% CI	42.06 to 47.33	48.38 to 54.07	50.81 to 55.40	39.18 to 50.13	54.35 to 61.59	48.95 to 65.87
Physical functioning						
Median (IQR)	23.09 (19.26–26.92)	46.06 (37.45–51.80)	46.06 (34.58–53.71)	24.05 (22.14–31.71)	53.71 (46.06–57.54)	48.93 (46.06–55.63)
95% CI	23.57 to 27.18	40.55 to 46.71	40.65 to 47.25	20.91 to 31.97	46.72 to 57.42	31.41 to 60.71
Role limitations owing to emotional health						
Median (IQR)	38.76 (28.31–56.17)	56.17 (35.28–56.17)	56.17 (43.98–56.17)	40.50 (35.28–54.43)	56.17 (49.20–56.17)	54.43 (49.20–56.17)
95% CI	36.46 to 43.66	42.30 to 49.82	45.66 to 52.02	30.87 to 52.75	49.64 to 57.72	36.34 to 62.07
Role limitations owing to physical health						
Median (IQR)	25.72 (21.23–32.46)	43.68 (33.58–52.66)	47.05 (35.83–54.91)	30.21 (25.72–39.20)	57.16 (41.44–57.16)	49.30 (41.44–57.16)
95% CI	25.87 to 29.79	39.06 to 45.37	41.79 to 48.01	24.62 to 40.29	42.65 to 58.19	31.79 to 60.07
Social functioning						
Median (IQR)	27.26 (22.25–37.29)	52.33 (37.29–57.34)	47.31 (39.80–57.34)	37.29 (24.76–39.80)	57.34 (52.33–57.34)	52.33 (47.31–57.34)
95% CI	27.83 to 33.73	43.24 to 50.04	44.77 to 50.48	25.00 to 40.80	50.83 to 58.12	33.87 to 62.43
Vitality						
Median (IQR)	31.80 (28.83–40.72)	55.57 (40.72–61.51)	52.60 (46.66–58.54)	36.26 (34.77–42.20)	55.57 (46.66–61.51)	60.03 (55.57–70.42)
95% CI	32.29 to 36.37	48.25 to 55.23	49.67 to 55.28	31.29 to 44.94	48.16 to 63.83	41.45 to 73.65

TABLE 24 Short Form questionnaire-36 items measurements by study group at each time point

Time and category	Number at risk	Number of patients measured in group	Minimum	Maximum	Median	IQR	95% CI
Baseline							
EVLP	18						
SF-36 MCS		8	31.49	57.42	43.46	41.49–47.31	37.96 to 50.40
SF-36 PCS		8	22.70	45.68	29.50	24.98–37.19	24.55 to 38.38
Standard	184						
SF-36 MCS		67	18.93	69.36	40.96	33.73–54.05	40.52 to 46.40
SF-36 PCS		67	13.19	51.12	27.61	22.30–30.94	25.39 to 29.02
3 months							
EVLP	14						
SF-36 MCS		7	50.05	59.45	58.18	57.30–59.43	54.21 to 60.25
SF-36 PCS		7	41.16	59.50	48.68	47.17–59.19	44.92 to 57.60
Standard	172						
SF-36 MCS		52	23.58	65.62	55.70	42.4–60.08	47.73 to 54.35
SF-36 PCS		52	25.82	59.45	45.47	38.36–50.07	41.22 to 46.26
12 months							
EVLP	12						
SF-36 MCS		6	33.32	62.80	58.96	53.06–62.19	43.19 to 66.57
SF-36 PCS		6	34.56	59.91	52.41	46.39–56.37	40.94 to 59.74
Standard	147						
SF-36 MCS		48	33.79	68.47	54.92	45.79–59.51	50.24 to 55.42
SF-36 PCS		48	24.22	60.40	47.69	36.18–54.08	42.47 to 48.27

The results show a general increase in the mean scores of the eight SF-36 domains from baseline to 12 months post transplant (see *Table 23*). The two domains that show the biggest increase in their scores are general health and vitality. Furthermore, although the physical functioning, role limitations owing to physical health and social functioning domains appear to show the same increase after 3 and 12 months from the day of the surgery in the standard arm of the study, they appear to increase at 3 months and then decrease at 12 months for the EVLP arm. The data are, however, too few for the relevance of this change to be sensibly interpreted. Similarly, the same pattern is seen for the general mental health and role limitations owing to emotional health dimensions. For the bodily pain domain there was a slight drop, on average, at 3 months and then an increase at 12 months for the EVLP arm. Nevertheless, the fact that few data are available for these three domains means that further interpretation must be done with caution.

The values of both the SF-36 summary measures, namely MCS and PCS, increase after transplant no matter which transplant procedure was performed. These data are presented in *Table 24*, and graphically in the box plots in *Figures 15* and *16*. In other words, the HRQoL of the patients improves throughout the follow-up of the lung recipients. In the standard procedure, the mean MCS score of the lung recipients increases from 43.5 at baseline to 51.0 at 3 months post transplant and 52.8 at 12 months post transplant, whereas the mean PCS score increases from 27.2 at baseline to 43.7 and 45.4 at 3 and 12 months, respectively. As far as the EVLP group is concerned, the mean MCS score changes from 44.2 at baseline to 57.2 at 3 months post

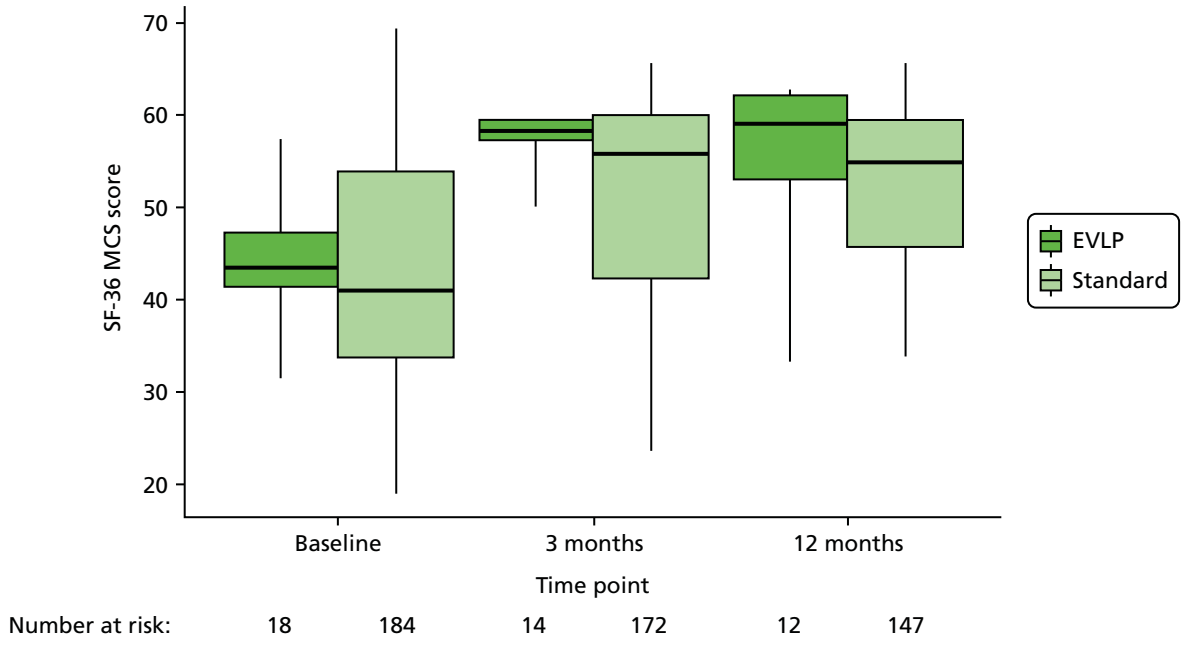

FIGURE 15 Box plot of SF-36 MCS scores, by study group and time point.

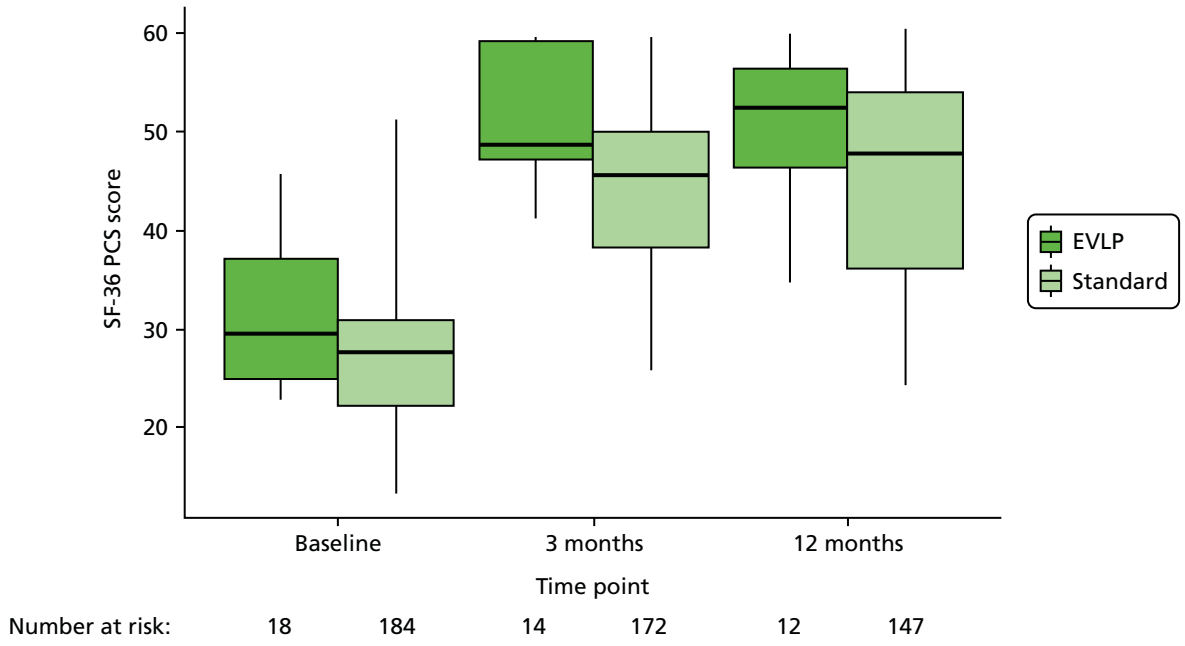

FIGURE 16 Box plot of SF-36 PCS scores, by study group and time point.

transplant and 54.9 at 12 months post transplant, whereas the mean PCS score increases from 31.5 to 51.3 at 3 months after the transplant and drops slightly to 50.3 at 12 months' follow-up. This slight decrease in the mean 12-month MCS and PCS scores in the EVLP arm of the study is consistent with the decrease in the scores for most of the eight domains at this time point. As mentioned above, any results regarding the effectiveness of the EVLP based on these scores given would not be reliable because of the very limited number of data available.

Examining the effect of ex vivo lung perfusion on the overall survival of patients awaiting transplantation

To capture the effects that an increased availability of donor organs due to EVLP might have on the survival of patients awaiting lung transplantation, waiting time in each of the two treatment groups was compared, and then waiting time in each group was compared with survival of those remaining on the waiting list. Waiting time is defined as the time from the date the participant is placed on the waiting list until the date transplant is performed. The waiting times until transplantation in the two study groups is shown in *Table 25*.

The median waiting time for standard transplant was 197 days (IQR 95–373 days), whereas the median waiting time for a transplant using an EVLP donor was 142 days (IQR 60–199 days), as shown in *Table 25*. There was a median difference of 55 days between transplant groups, showing a reduction in waiting time if having a transplant using an EVLP-assessed donor organ. This is also illustrated by *Figure 17*, which shows a maximum waiting time of 551 days for transplant using a EVLP donor compared with a maximum waiting time of 2143 days for a standard transplant. A log-rank test for difference in waiting times between transplant type using the Kaplan–Meier estimates gave a *p*-value of 0.042, which shows a significant difference in waiting times between the two groups. However, these findings should be interpreted with caution, in view of the small numbers of patients in the EVLP group.

Survival from listing

To assess overall survival between transplant groups and those remaining on the waiting list, the time from being placed on the waiting list until 12 months post transplant or 1 May 2015, with censoring for death or loss to follow-up, is presented in *Table 26*. Waiting list dates were collated for all participants during recruitment to the study; however, for those remaining on the waiting list, some of this information was not collated. For these participants, waiting list dates were obtained from the NHSBT registry.

TABLE 25 Summary of waiting time until transplant

	Waiting time (days)					
Transplant type	Mean	SD	Median	IQR	Minimum	Maximum
Standard ($n = 184$)	307	348	197	95–373	6	2143
EVLP ($n = 18$)	178	156	142	60–199	9	551
Total ($N = 202$)	296	337	184	93–367	6	2143

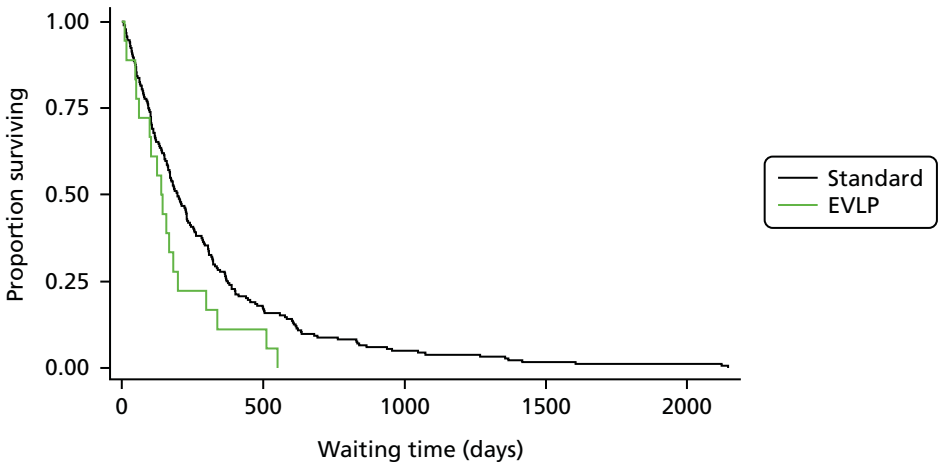

FIGURE 17 Kaplan–Meier graph of waiting time until transplant by transplant type (each event in this graph indicates a transplant performed).

TABLE 26 Summary of survival time from listing

	Survival time (days)					
Group	Mean	SD	Media	IQR	Minimum	Maximum
Standard ($n = 184$)	631	362	536	429–703	46	2508
EVLP ($n = 18$)	453	197	479	412–543	73	916
No transplant ($n = 212$)	621	438	543	324–830	18	2867
Total ($N = 414$)	618	399	535	394–741	18	2867

For the purpose of this analysis, 1 May 2015 was chosen as the end date for those who did not have a transplant, since this is approximately 12 months after the last transplant was performed. Of the 232 participants remaining on the waiting list, 20 have been excluded from the analysis. Thirteen were excluded because they were recruited to another study in which they had a transplant, four were excluded because they no longer wanted to be part of the study and three were excluded because there is no record of the date they were removed from the waiting list. Thirty-nine participants who were included in the analysis have been censored: 11 of these were censored by the date they were removed from the waiting list or were lost to follow-up and 28 were censored by the date on which they had a transplant outside of this trial. There were 41 participants for whom we had been unable to confirm their status as of 1 May 2015. Since we have not received information regarding their death (which we would have expected), we have assumed these participants remained on the waiting list on 1 May 2015.

The Kaplan–Meier estimates of survival from being placed on the transplant list to transplant or death/censoring are shown in *Figure 18* for the three study groups. The median survival time from listing was 536 days (IQR 429–703 days), 479 days (IQR 412–543 days) and 543 days (IQR 324–830 days) for standard transplant, EVLP transplant and waiting list groups, respectively (see *Table 26*). The log-rank test of difference in survival times was significant ($p = 0.007$), implying that those having a standard lung transplant had better survival than those who remained on the waiting list and those having an EVLP transplant. However, these findings should be interpreted with caution in view of possible selection bias and the small number of patients in the EVLP group.

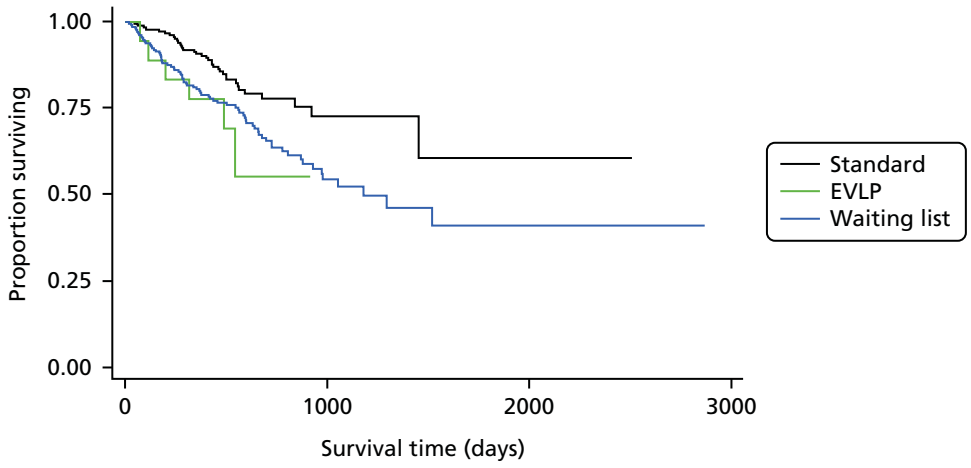

FIGURE 18 Kaplan–Meier graph of survival time from being placed on the transplant waiting list.

Identifying clinical predictors of successful ex vivo lung perfusion reconditioning

Between 1 April 2012 and 9 July 2014, lungs from 53 UK multiorgan donors were identified as unsuitable for immediate standard transplantation despite extensive donor management. These donors all satisfied the strict entry criteria for inclusion in the EVLP arm of the study (*Boxes 1* and *2*).

BOX 1 Criteria for EVLP assessment and reconditioning: using DBD or DCD lungs

Any one or more of the following

- Warm ischaemic time > 30 minutes for DCD donors.
- Withdrawal of life support between 60 and 90 minutes for DCD donors.
- Chest radiograph findings prohibitive of standard transplantation.
- Systemic arterial PaO_2 < 300 mmHg and/or selective pulmonary vein gas < 225 mmHg 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 endotracheal 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 > 10–12 hours and prevent donor organ use, such as:
  - viral studies awaited
  - HLA compatibility studies
  - pathology assessment of indeterminate mass in any donor
  - awaiting recipient admission.

PaO_2, partial pressure of oxygen; PEEP, positive end-expiratory pressure.

BOX 2 Absolute contraindications to donor lung use for standard transplant or for EVLP

Any one of the following

- Donor aged > 65 years.
- Donor HIV positive or other contraindicated infection risk (e.g. 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 intrapleural thoracic surgery or dense adhesions prohibiting safe lung procurement.
- Confirmation of malignancy within 5 years (excluding central nervous system malignancies).

HIV, human immunodeficiency virus.

Of these 53 donors, 35 died from spontaneous intracranial haemorrhage (66%), eight from hypoxic brain injury (15%), five from traumatic brain injury (9%), three from thrombotic stroke (6%), one from an expansive brain tumour (2%) and one from meningitis (2%). The donor lungs were procured in a routine fashion and transported on ice to the accepting institution. A total of 27 (51%) were assessed in Newcastle, nine in Harefield (17%), seven in Manchester (13%), six in Birmingham (11%) and four in Papworth (8%). Fourteen donor lungs were from donors without a circulation (DCD) (Maastricht category III, 26%) and 39 were from brain-dead donors (DBD) (Maastricht category IV, 74%). The EVLP assessments were evenly distributed between donor sexes [26 female (49%) and 27 male (51%)] and the median donor age was 50 years (range 16–65 years). If one lung did not meet entry criteria and was deemed unusable because of severe consolidation or extensive contusion on inspection, or if the intended recipient was for a specific side (i.e. single-lung transplant), only one lung was procured. Fifty lungs (94%) were perfused as double lungs and three (6%) as singles (two right lungs and one left lung). They were assessed for a median time of 175 minutes (range 73–383 minutes) while being normothermically perfused on the Vivoline LS1 EVLP circuit.

The study protocol allowed for lungs that satisfied certain criteria, as outlined in *Box 1*, to be assessed using EVLP. The primary indications for EVLP assessment were grouped into three general categories: 35 donor lungs (66%) were found unsuitable for standard transplantation because of poor lung function with an optimised donor ratio of arterial partial pressure of oxygen (PaO_2) – shown throughout the report as kPa (mmHg) – to $FiO_2 < 40$ (300) and/or a selective pulmonary vein gas < 30 (225) with a FiO_2 of 1.0 (100%) at procurement; 13 lungs (25%) were turned down as a result of abnormalities during inspection (pulmonary oedema, abnormal bronchoscopy, extensive atelectasis, etc.); and three lungs (6%) were turned down for standard transplantation for logistical reasons. Some lungs were excluded from EVLP as they had absolute contraindications to transplant (see *Box 2*).

Of the donor lungs turned down for logistic purposes, two had a suspicious mass in need of urgent histological evaluation before a decision on transplant was made. One was revealed to be cancerous and the lungs were discarded after an otherwise successful EVLP perfusion, and the other was confirmed benign and the lungs were transplanted. In one case, no theatre team was available as they had just started another transplantation. In this case, the lungs also remained stable or improved measurable physiological parameters during preservation on the EVLP circuit, but were in the end turned down for transplantation because of deteriorating oedema formation on inspection.

Of the 53 donors, 24 (45%) were current smokers, 18 (34%) had abnormal chest radiographs at the time of procurement and 22 (42%) had airway secretions deemed prohibitive of standard transplantation, predominantly purulent secretions. The median ventilation time for the EVLP donors before procurement was 2 days (range < 1–10.3 days) and 27 donors (51%) had positive microbiology cultures from sputum, BAL fluid or cerebrospinal fluid. The median optimised $PaO_2 : FiO_2$ ratio for the 53 EVLP donors at the time of procurement was 39.9 [299 (range 95–535 mmHg)] and after EVLP was 50.9 [381.5 (range 74–638 mmHg)]. The EVLP assessments followed one of two standardised perfusion protocols depending on when the lungs were entered into the study. Initially, between 1 April 2012 and 31 March 2013, a hybrid protocol combining elements of the Toronto and Lund protocols was used with an open left atrium, an acellular perfusate and a reduced perfusate flow to 40–60% of the donor's calculated cardiac output. After a pause midway through the study because of concerns over the rate of ECMO use in transplants performed after assessment using the hybrid EVLP protocol, the perfusion strategy was altered and the study was restarted in August 2013 and the hybrid protocol replaced by the Lund protocol.

The Lund protocol uses a cellular perfusate (haematocrit 10–15%) and a full-flow perfusion strategy (100% of cardiac output), but is otherwise identical to the hybrid protocol. The assessment and ventilation strategies, airway and vascular pressure limits, and perfusate composition was otherwise unaltered (*Table 27*).

TABLE 27 The DEVELOP-UK study EVLP protocols

Parameter	Protocol	
	Hybrid (1 April 2012–31 March 2013)	Lund (1 August 2013–9 July 2014)
Perfusion		
Target flow	40–60% of cardiac output	100% of cardiac output (70 ml/kg/minute)
Pulmonary arterial pressure	< 20 mmHg	< 20 mmHg
Left atrial pressure	0 mmHg (open left atrium)	0 mmHg (open left atrium)
Pump	Roller	Roller
Perfusate	2 l of Steen Solution	2 l of Steen Solution with red cell concentrates (haematocrit 10–15%)
Ventilation		
Mode	Volume controlled	Volume controlled
Tidal volume	6–8 ml/kg	6–8 ml/kg
Frequency	10–15 b.p.m.	10–15 b.p.m.
Positive end-expiratory pressure	5 cmH_2O	5 cmH_2O
FiO_2	50%	50%
Temperature		
Start of ventilation	32 °C	32 °C
Start of perfusion	15 °C	15 °C
Start of evaluation	37 °C	37 °C

b.p.m., beats per minute.

Lung performance during ex vivo lung perfusion assessment

Transplant suitability was assessed as soon as the lungs had stabilised, at 37 °C and perfusing at full flow, and thereafter hourly until the end of perfusion. Lungs meeting transplant suitability at any time point were cooled and transplanted (*Boxes 3* and *4*). Lungs deemed to have futile prospects for improvement were taken off the circuit and discarded.

BOX 3 Criteria for transplant after successful EVLP assessment and reconditioning

All of the following

- Any DBD or DCD donor lungs meeting previously stated criteria for standard transplant.
- Pulmonary artery pressure < 20 mmHg, while achieving target perfusate flow.
- Oxygen capacity shown by ΔPaO_2 of > 300 mmHg (perfusate left atrium PaO_2 – perfusate pulmonary artery PaO_2)/FiO_2.
- Selective pulmonary vein gas > 225 mmHg on 100% FiO_2 and 5 cmH_2O PEEP.
- Stable or improving lung compliance and stable or falling lung resistance.
- No pulmonary oedema build-up in the endotracheal tube.
- Satisfactory assessment on inspection and palpation.
- Confirmed reconsent of potential matched recipient to receive an EVLP-reconditioned lung.

PEEP, positive end-expiratory pressure.

BOX 4 Criteria for failed EVLP assessment and reconditioning: transplant will not proceed

Any of the following

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

The performance of the 53 donor lungs undergoing EVLP assessment in the study is reported in two different ways to give as robust a description as possible of this cohort.

First, clinical EVLP success was defined as any EVLP-assessed donor lung deemed clinically suitable for transplantation at the end of perfusion by the surgical team performing the assessment ($n = 22$). This included all EVLP lungs that were transplanted within the study ($n = 18$) and all lungs that were accepted for transplantation on the basis of EVLP performance, but had to be turned down due to unforeseen logistical reasons ($n = 4$) (*Figure 19*).

Of these four cases, one pair of lungs accepted for double lung transplant had to be discarded as the recipient presented with an active airway infection and was found to be at too high risk for the operation on arrival at the hospital. The lungs were offered on urgently, but turned down by all UK centres owing to logistics. One lung had an unreported irreparable left pulmonary artery laceration with haematoma formation from the retrieval surgery. The right lung was selectively perfused and deemed suitable for transplantation. There was, at this point, no available matching single lung recipient and the lung had to be discarded after having been offered on to all other UK centres. One left single lung accepted for transplantation for a matched recipient had to be aborted due to an emergency in theatres and lack of additional surgical capacity at the site. One lung was put on EVLP for logistical reasons while awaiting histology of suspicious masses found during the organ procurement. Evaluation of a liver nodule showed chronic lymphatic lymphoma. Although the lung biopsy was found benign, the transplant was aborted because of the elevated risk of tumour transmission to the recipient. The lungs were meanwhile successfully reconditioned on the circuit and deemed to be in a suitable condition for transplant had it not been for the histological liver findings.

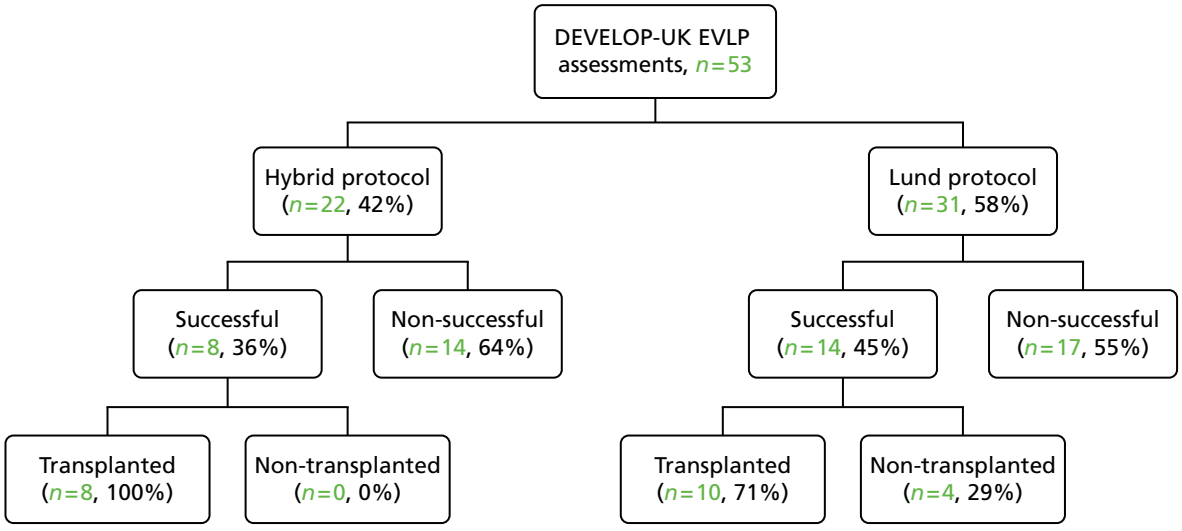

FIGURE 19 Flow chart for clinical EVLP success ($n = 22$).

Second, per-protocol success was defined as all perfused donor lungs meeting the complete set of predefined study criteria for EVLP success, regardless of clinical transplant result ($n = 17$). This included all EVLP lungs that were transplanted in the study while meeting all predefined transplant criteria ($n = 13$) and all non-transplanted EVLP lungs that met all transplant criteria but were discarded purely on logistical grounds ($n = 4$) (*Figure 20*).

Of the 18 EVLP lungs that were transplanted in the study, five had to be defined as per-protocol non-successful perfusions as, although deemed clinically suitable for transplantation, they failed to meet all predefined transplant criteria and were transplanted as a result of a protocol violation.

Two of these five lungs were transplanted even though their mixed pulmonary vein $PaO_2 : FiO_2$ ratio was 40.0 (< 300) during the assessment. One of these almost doubled its optimised retrieval $PaO_2 : FiO_2$ ratio during the perfusion, increasing from 22.0 (166) to 38.6 (290), and the other had a recorded mixed pulmonary vein $PaO_2 : FiO_2$ ratio of 35 (262), while all selective pulmonary vein gases were well above the study cut-off point [range 46.0–72.0 (345–540)]. Three EVLP lungs were transplanted while having one or two selective lower lobe pulmonary vein gases < 30 (225); however, their mixed pulmonary vein $PaO_2 : FiO_2$ met the study transplant criterion of > 40 (300). All five of these lungs were subsequently transplanted into recipients with satisfying post-transplant outcomes and a 100% 1-year survival. Of the 13 recipients receiving lungs that met all study criteria for transplantation, only seven (54%) remained alive 12 months post transplant.

Logistic regression analyses

A logistic regression approach was used to examine the association between successful reconditioning (defined on either of the bases explained above) and a number of potential predictors based on donor characteristics and indices measured during EVLP. As a result of the lower than planned numbers in the EVLP arm, the work here must be regarded as exploratory in nature rather than definitive.

In terms of the variables to be considered for the examination of potential predictors of successful EVLP, univariate exact logistic regression models were fitted with successful EVLP as the dependent variable, and each of the following in turn as the independent variable. These models were fitted using the exlogistic option in Stata® 13.1 (StataCorp LP, TX, USA):

- donor {age, sex, cause of death, smoking history, ischaemic time, duration of ventilation, oxygenation, donor type [after brain death (DBD) or after circulatory death (DCD)]}
- EVLP physiology (oxygenation, lung compliance and resistance, airway pressure, perfusion time).

The original intent was also to use similar approaches to examine EVLP donor lungs used in transplantation and the association between early clinical outcome measures in recipients and physiological indices measured during EVLP. However, having only 18 patients in the EVLP transplant group meant that such an analysis would not be statistically meaningful.

Table 28 gives the results of the univariate analyses of predictors of clinical EVLP success. Here odds ratios are presented for different categories or, in the case of continuous variables, based on a unit increase in the variable. Although some of the point estimates for odds ratios varied somewhat from one, in all instances the associated 95% CI included one.

Table 29 shows the results from the corresponding analyses, based on per-protocol success. The odds ratios and CIs are very similar to those based on clinical EVLP success.

In conclusion, there was no strong evidence to indicate specific predictors of successful EVLP reconditioning. However, the analyses were restricted by the relatively small numbers.

FIGURE 20 The flow chart for per-protocol EVLP success ($n = 17$).

TABLE 28 Univariate exact logistic regression analysis of predictors of successful EVLP reconditioning (clinical EVLP success)

Variable	Category or units	Number of patients in category	Number of successes	OR (95% CI)
EVLP protocol	Lund	31	14	1
	Hybrid	22	8	0.70 (0.19 to 2.43)
Donor age (years)	Based on a 10-year increase	53	22	1.46 (0.90 to 2.50)
Sex (reference category: males)	Females	26	9	0.58 (0.16 to 1.97)
	Males	27	13	1
Smoking (reference category: non-smokers)	Non-smokers	29	13	1
	Smokers	24	9	0.74 (0.21 to 2.54)
Ischaemic time (hours)	Based on a 1-hour increase	48	21	1.00 (0.61 to 1.64)
Duration of ventilation (days)	Based on a 1-day increase	53	22	1.17 (0.87 to 1.63)
Optimised donor $PaO_2 : FiO_2$ ratio before EVLP	Based on a 100-mmHg increase	53	22	0.81 (0.50 to 1.27)
Donor type (reference category: DBD)	DBD	39	17	1
	DCD	14	5	0.72 (0.16 to 2.96)
$PaO_2 : FiO_2$ after EVLP	Based on a 100-mmHg increase	48	22	1.34 (0.86 to 2.15)
Compliance start (ml/mbar)	Based on a 10 ml/mbar increase	28	15	1.25 (0.94 to 1.72)
Change in compliance (ml/mbar)[a]	Based on a 10 ml/mbar increase	15	7	0.98 (0.52 to 1.88)
Airway resistance start	Based on a 1 mbar/l/second increase	24	11	0.93 (0.77 to 1.00)
Change in airway resistance[a]	Based on a 1 mbar/l/second increase	12	4	2.11 (0.95 to 19.99)
Peak airway pressure start	Based on a 1-cmH_2O increase	41	18	0.88 (0.73 to 1.05)
Change in peak airway pressure[a]	Based on a 1-cmH_2O increase	24	9	1.06 (0.85 to 1.35)
EVLP time	Based on a 1-hour increase	49	20	0.95 (0.54 to 1.65)

OR, odds ratio.
a Changes defined as start–end.

Archiving

The trial data were stored on the Newcastle Clinical Trials Unit's MACRO database system, provided by Infermed's MACRO software as a service system. The hardware was located at their hosting partner Rackspace's secure premises in London, UK, and is managed and supported by the Rackspace team. All data were stored and transmitted securely. Data were hosted and backed up only in the UK and were never transferred overseas. Only authorised staff can grant and have control of access. Any snapshots of the database taken will be kept on the Newcastle University server, which is backed up daily.

Once all trial-related analysis and activities are completed, the database will remain on MACRO, with permissions removed. The data will be archived onto disk for each site file and also centrally in accordance with the Newcastle Clinical Trials Unit's standard operating procedures (SOPs).

TABLE 29 Univariate exact logistic regression analysis of predictors of successful EVLP reconditioning (per-protocol success)

Variable	Category or units	Number of patients in category	Number of successes	OR (95% CI)
EVLP type	Lund	31	6	1
	Hybrid	22	11	0.69 (0.17 to 2.58)
Donor age (years)	Based on a 10-year increase	53	17	1.58 (0.92 to 2.93)
Sex (reference category: males)	Females	26	8	0.89 (0.24 to 3.28)
	Males	27	9	1
Smoking (reference category: non-smokers)	Non-smokers	29	10	1
	Smokers	24	7	0.79 (0.20 to 2.90)
Ischaemic time (hours)	Based on a 1-hour increase	48	17	0.80 (0.45 to 1.33)
Duration of ventilation (days)	Based on a 1-day increase	53	17	0.97 (0.68 to 1.32)
Optimised donor P/F before EVLP	Based on a 100-mmHg increase	53	17	0.86 (0.52 to 1.39)
Donor type (reference category: DBD)	DBD	39	14	1
	DCD	14	3	0.49 (0.08 to 2.32)
PF after EVLP	Based on a 100-mmHg increase	48	17	1.59 (0.97 to 2.77)
Compliance start (ml/mbar)	Based on a 10 ml/mbar increase	28	13	1.10 (0.84 to 1.47)
Change in compliance (ml/mbar)[a]	Based on a 10 ml/mbar increase	15	6	1.02 (0.54 to 2.00)
Airway resistance start	Based on a 1 mbar/l/second increase	24	9	0.98 (0.82 to 1.01)
Change in airway resistance[a]	Based on a 1 mbar/l/second increase	12	3	2.70 (0.95 to 58.58)
Peak airway pressure start	Based on a 1-cmH_2O increase	41	14	0.83 (0.66 to 1.01)
Change in peak airway pressure[a]	Based on a 1-cmH_2O increase	24	7	1.07 (0.84 to 1.36)
EVLP time (hours)	Based on a 1-hour increase	49	17	0.93 (0.51 to 1.65)

OR, odds ratio.
a Changes defined as start–end.

Chapter 4 Economic evaluation

Overall aims of the economic evaluation

The original aim of the economic analysis of the DEVELOP-UK study was to estimate the cost-effectiveness of EVLP compared with standard donor lung transplantation. Cost-effectiveness was to be estimated in terms of the incremental cost per quality-adjusted life-year (QALY) gained and compared with the current National Institute for Health and Care Excellence (NICE) cost-effectiveness threshold (£20,000 per QALY). This analysis was to take the form of a within-study economic evaluation and a model to extrapolate findings over patients' lifetime. As previously described, the DEVELOP-UK study was terminated before the target participant recruitment was reached. Therefore, the originally planned economic evaluation of the study was conducted with a few changes within its initial design.

Given the smaller than planned recruitment numbers in the EVLP arm of the study, the aims of the economic section were recast to:

1. provide a descriptive 'within-study' analysis of the available data in terms of costs and QALYs for both EVLP and standard donor lung transplantation, without directly comparing the two procedures
2. estimate a regression model to explore predictors of NHS costs for transplants that may aid future modelling studies involving a lung transplant as one of the events of interest
3. report an exploratory economic model populated for both types of lung transplantation (standard and EVLP) with data obtained from the relevant literature and from the DEVELOP-UK study.

Within-study descriptive analysis of costs and quality-adjusted life-years

There are five parts of analysis that were proposed to be presented in this element of the study. First, the unit costs and the sources of these costs for standard donor and EVLP lung transplantation were to be described. Second, an analysis of the resource use was to be conducted to estimate the mean (SD) and the median (IQR) use of each type of resource. In the third part of the analysis, resource use and unit cost data were to be combined in order to estimate the average cost for each area of resource use and in total for each one of the two types of transplantation. The fourth part of the analysis that gives information on HRQoL was to be used to estimate QALYs for each type of transplantation based on the responses of the participants to the SF-36. Fifth, and finally, the net benefits of standard and EVLP lung transplantation were to be calculated based on the costs and QALYs of the two different approaches to achieving a lung transplant.

As the study was terminated early because of a lack of patient recruitment in one of its two arms, it was agreed that no direct within-study comparison would be drawn in terms of cost-effectiveness, and that the presentation of results would be limited to descriptive data. These descriptive data were, however, used to populate an exploratory economic model.

Methods

Outline of the lung transplant procedure

First of all, one of the most important parts of any economic evaluation is to understand the process of care, so as to fully understand what costs and outcomes should be included in the analysis. The first stage of the process is the notification of potential organ donors. In other words, it is necessary for every NHS hospital to identify any potential donors that might exist within its patient population. In this case, the donation of a lung might be after circulatory death (DCD) or brain death (DBD) of the donor. The donor's

hospital is also responsible for informing its local SNOD from NHSBT about the existence of a single- or a multiple-organ donor on its premises. NHSBT would then assess the donor and contact the local transplant centre for them to check its waiting list records in order to find the most suitable organ recipients for that donor. Once a transplant centre is contacted by NHSBT about a possible donor, it should investigate whether or not there are any patients on its lung transplant waiting list that have the necessary size and tissue characteristics that match those of the donor. Here, it is important to mention that the patients who are included in a hospital's waiting list are frequently monitored in order to ensure that the most appropriate patient will be chosen in case a lung transplant becomes available in the future.

After contacting the SNOD in order to receive more information regarding the condition and the characteristics of the donor, the transplant centre may send a scout – if the donor hospital is less than 2 hours away – and, subsequently, a retrieval team to potentially collect the donor lung(s). Following the initial assessment of the lung by the retrieval team, and assuming that it is in a suitable condition to proceed to transplant, the retrieval team sends the organ back to the transplant site. For the purposes of the study, during the period of time that the study was under way, the retrieval team should have also considered whether or not an unusable lung (i.e. a lung that would not be retrieved otherwise based on standard tests and the subjective assessment of the retrieval surgeon) could be assessed and reconditioned by EVLP in order to be used as a transplant in the EVLP arm of the study. If so, retrieval was performed with the intention that this lung would be transplanted using EVLP. In addition, during the same period of time, more retrieval teams were sent out than normal because there was a higher probability that a lung would be accepted for a transplant.

Here, it should be mentioned that during a usual retrieval, several organs might be retrieved (e.g. heart, kidney, pancreas and liver). It should also be noted that at times no retrieval might be performed if the team decides differently. During this study, 53 lungs were retrieved in order to undergo an EVLP procedure. Of these lungs, only 18 were reconditioned successfully and transplanted at the end. The remainder were not considered appropriate for transplantation at the transplant site. Therefore, in the analysis of this study, the ratio of EVLP transplant per retrieval was considered to be equal to 18 EVLP lungs out of 53 attempts. On the other hand, for the standard arm of the study, it was difficult to calculate the number of lungs assessed but not retrieved given the parameters described above. However, expert opinion from the study team advised that each time a lung is assessed as suitable for transplant, this lung is always transplanted. Consequently, it was assumed that each time a retrieval team was sent to a donor's hospital a lung was retrieved and sent back to the transplant site in order to be assessed and transplanted.

At the same time as a retrieval team has been dispatched to the donor hospital, the transplant centre should contact the potential recipient in order to inform them about the possibility of a transplant happening. Sometimes, more than one patient is contacted in order to ensure that the lung will be transplanted in the event that one of them has a current infection and cannot be transplanted. Once the intended recipient(s) arrives at the transplant site, the recipient meets with the transplant co-ordinator to receive more information about the transplant, and is prepared for the transplant. In the case of an EVLP lung transplant, the EVLP procedure may be started before the recipient arrives at the hospital and continue while the patient is being prepared for the surgery.

Afterwards, the lung transplant operation is under way, where exactly the same procedure for both standard and EVLP transplants is followed. After the operation, the lung recipient is admitted to the ITU and then onto the transplant ward in order to receive the necessary post-operative care and manage any complications that might occur. Following hospital discharge, and assuming there are no complications, infections or rejection episodes necessitating readmission, the recipient returns to the hospital every month (or less depending on the clinicians' recommendations) for routine tests (i.e. blood test, bronchoscopy, etc.) and in order to report any complications. In between, the lung recipient might also visit a GP to report any new symptoms or AEs from the medications given.

Study perspective

The perspective of the study (i.e. which costs and outcomes were considered in the analysis) was the national health-care provider (the UK NHS). The duration of follow-up was 12 months following transplant, with outpatient visits planned at 1, 3, 6 and 12 months post transplant.

Cost and use of resources

The data collected on costs were categorised into the following areas based on when the resources were used during the study: donor's hospital, lung retrieval, transplant preparation, EVLP procedure, lung transplant, post-operative care, outpatient care and concomitant medications.

Donor's hospital

As mentioned above, the donor's hospital is responsible for contacting the NHSBT to report any potential lung donors. Before the retrieval team arrives, the SNOD should have performed an initial assessment to provide the patient's history to the transplant team. This assessment consists of several routine tests, such as a full blood count (FBC) and chest radiography, as well as, sometimes, a bronchoscopy procedure. The cost of the initial assessment was derived from the costing tool of Newcastle upon Tyne Hospitals (NuTH; obtained from: www.newcastlejro.org.uk) or the *NHS Reference Costs 2013/2014*,[49] while the information regarding the use of each test was obtained from the CRFs of the study or the hospital staff (personal communications: Mr Tanveer Butt, NuTH, June 2015; Ms Alison Davison, NuTH, June 2015; Mr Paul Henderson, NuTH, September 2014; and Ms Katie Morley, NuTH, October 2014). The hospital staff should also administer a single dose of methylprednisolone (500 mg, 1 g or 2 g, with the dose decided based on the donor's weight) to modulate the pulmonary inflammatory activity of the donor. The use of methylprednisolone was reported on the CRF, while its cost was collected from the *British National Formulary* (BNF) for each dose that was administered.[50]

Lung retrieval

Lung retrieval begins when the scout team and/or the retrieval team arrives at the donor's hospital. Normally, a scout team is sent out if the donor's hospital is within a 2-hour range from the transplant site in order to make an initial examination of the organ. According to the retrieval team of NuTH (Mr Tanveer Butt, NuTH, September 2014, personal communication), around one-fifth of lung retrievals are scouted first. The scout team consists of a retrieval surgeon (clinical fellow) and a scrub nurse (band 7), while in the retrieval team a perfusionist (band 7) is also included. The retrieval process was estimated, based on clinical advice, to last for approximately 9 hours, with a further 4 hours added if a scouting is performed (one in five cases). All the costs of the staff were obtained from the Personal Social Services Research Unit (PSSRU)'s *Unit Costs of Health and Social Care 2014*,[51] while the resource information came from the NuTH retrieval team (personal communications: Mr Tanveer Butt, NuTH, September 2014; and Mr Paul Henderson, NuTH, September 2014).

As far as the travelling of the two teams is concerned, this is variable and depends on the distance of the donor's hospital from the transplant site. According to the NuTH NHS staff (Mr Brian Leadbitter, NuTH NHS, June 2015, personal communication), a scout team always travels by road while a retrieval team travels by road in 74% of the cases, and by road and air in 26% of the cases. Once the lung is retrieved, it might be returned to the transplant centre either by road (50%), or by road and air (50%). The usage and costs of travel were based on the cardiothoracic organ retrieval invoices given by the NHS staff of NuTH.

During the lung retrieval, the team requests the donor's medical history and the screening tests provided by the hospital staff [i.e. ABG, electrocardiography (ECG), etc.]. Then the team performs an initial assessment of the patient in order to examine whether or not the lung can be transplanted. There are three diagnostic tests that are normally performed by the retrieval team: chest radiography, an ABG test and a bronchoscopy. Here, it should be mentioned that an ABG test is provided only when the lung comes from a DBD donor; in cases of a DCD this test cannot be performed as the heart has already stopped (Mr Tanveer Butt, NuTH, September 2014, personal communication).

Chest radiography is performed with the donor hospital's equipment and, for the purposes of the analysis, its cost was derived from the NuTH costing tool (obtained from: www.newcastlejro.org.uk) while its use was reported on the CRF. For the ABG test and the bronchoscopy procedure, the retrieval team takes the necessary equipment with them. According to the NuTH retrieval team's checklist (personal communications: Mr Tanveer Butt, NuTH, September 2014; and Mr Paul Henderson, NuTH, September 2014), the team always brings a bronchoscope, strapple tape and 0.5% chlorhexidine spray to the donor's hospital. In addition to these pieces of equipment, a different number of 0.9% sodium chloride solutions might be needed during the retrieval, and these are usually provided by the donor's hospital. In the case of a DBD donor, the donor's hospital also provides the necessary equipment for the ABG test (i.e. vacutainers, syringes, portable clinical analyser, etc.).

The costs of most of this equipment used by the retrieval team were obtained from the official websites of the resective medical suppliers. In the case of the bronchoscope and the clinical analyser for blood analysis (i-STAT® device, Abbott Laboratories, Dallas, TX, USA), their equivalent annual costs were estimated based on the life expectancy of the equipment, assuming a 3.5% discount rate.[52] The equivalent annual cost was then divided by the expected annual usage to get a cost per recipient. The cost of the i-STAT test cartridges, which are the testing cartridges used during a diagnostic test with an i-STAT clinical analyser, was obtained from the retrieval team, and the cost of sodium bicarbonate was obtained from the BNF 2014.[50]

The perfusionist member of the team is responsible for measuring the breathing (ventilation) and circulation (perfusion) in all areas of the lung retrieved, as well as ensuring the proper maintenance of the organ. In order to increase the cooling, preservation and storage of the lungs, a colloid preservation solution (PERFADEX) is needed. To be more precise, 2.8 l of PERFADEX solution is needed antegrade for lung preservation, whereas 1 l is given retrograde on the back table just after the harvest procedure (250 ml into each of the four veins of the lung). To each litre of this solution, a sterile sodium salt, epoprostenol sodium (FLOLAN®, GlaxoSmithKline), THAM, $CaCl_2$ and heparin sodium are added. The use of the first three was reported by the retrieval team (personal communications: Mr Tanveer Butt, NuTH, September 2014; and Mr Paul Henderson, NuTH, September 2014), whereas for heparin sodium and $CaCl_2$ it was collected from the BNF 2014.[50] The costs of FLOLAN, THAM, heparin sodium and $CaCl_2$ were obtained from the BNF 2014,[50] whereas the price of the different dosages of PERFADEX solutions was given by its producer company, XVIVO Perfusion AB.

Transplant preparation

After the retrieval, the lung is delivered back to the transplant site in order to be prepared for the transplant. In case the lung needs to be reconditioned before the transplant, the EVLP procedure is also followed in parallel (see *Ex vivo lung perfusion procedure*). Meanwhile, the transplant co-ordinator is responsible for contacting the potential recipient(s) – this normally lasts for 1 hour. The potential recipient is selected from the transplant waiting list by the transplant surgeon on duty. The transplant surgeon on duty is ultimately responsible for deciding which patient meets the necessary criteria and has the appropriate characteristics that match with the donor's tissue in order to be transplanted (Professor Andrew Fisher, NuTH, November 2015, personal communication). It should also be noted that each patient on the waiting list receives frequent diagnostic tests, such as FBC and ECG, to monitor their condition. For the purposes of this study, the costs of these tests were not considered as part of the transplant cost.

Once the appropriate patient(s) are selected, they are transferred to the transplant centre by road or air depending on the accessibility to, and the distance from, the site. There are different ways that a patient might be transferred to the hospital, including ambulance, aeroplane (air ambulance) or private car. Nevertheless, during the analysis of the study, it was difficult to obtain more details regarding the resources used for the patient travelling to the transplant centres. As a result, this information was omitted from the estimation of costs.

At the transplant centre, the potential recipient(s) meets with the transplant co-ordinator for approximately 2 hours in order to receive more information regarding the transplant. Following this, a tissue typing

procedure is performed by NHSBT in order to test the compatibility between the tissue of the prospective donor and that of the potential recipient. The potential recipients will also receive the following tests to monitor their health status: ABG test, chest radiography and ECG. After these tests, the patient stays in the transplant centre ward until the operation (usually for 1 hour) or until sent home because the transplant has not progressed. During this time, medications tailored to the patient's health state are administered (e.g. specific antibiotic cocktail). Azathioprine (200 mg) is also given orally before the beginning of the transplant as part of the standard procedure (Professor Andrew Fisher, NuTH, June 2015, personal communication).

The time needed for the contact and meeting with the potential recipients(s), as well as the average waiting time, was sourced by the NuTH staff (personal communications: Ms Alison Davison, NuTH, June 2015; and Ms Katie Morley, NuTH, October 2014). The hospital staff also reported that a tissue typing test is performed after the meeting with the transplant co-ordinator, while an ECG is also provided before the transplant. The CRF reported that an ABG, a FBC and chest radiography are conducted as well. The PSSRU's *Unit Costs of Health and Social Care 2014*[51] gave the costs per hour for the transplant co-ordinator, while the cost of the hospital ward time was derived from the *NHS Reference Costs 2013/2014*.[49] The unit costs of all the diagnostic tests were obtained from the NuTH costing tool (obtained from www.newcastlejro.org.uk), apart from the cost of the tissue typing test that is provided by the Information Services Division (ISD)'s *ISD Scotland Theatre Services*.[53] In addition, the cost of azathioprine was collected from the BNF 2014.[50]

Ex vivo lung perfusion procedure

The EVLP is a procedure that needs, on average, 6 hours in order to be completed. For the EVLP, an operating theatre is required in which the whole procedure takes place. The cost per hour of an operating theatre came from ISD's *ISD Scotland Theatre Services*.[53] As far as the staff is concerned, a consultant surgeon, a surgical fellow, a scrub nurse (band 5), a perfusionist (band 7) and an anaesthetic registrar are needed for various amounts of time during the EVLP. The salary calculations for all the members of the staff were based on the PSSRU's *Unit Costs of Health and Social Care 2014*,[51] whereas the information regarding the staff time was given by the hospital staff and Vivoline Medical AB company (personal communications: Anders Andreasson, NuTH, September 2014; Anna Söderlund, Vivoline Medical AB, July 2014; Mr Paul Henderson, NuTH, September 2014; and Ms Katie Morley, NuTH, October 2014).

According to Vivoline Medical AB and the NuTH hospital staff (personal communications: Mr Anders Andreasson, NuTH, September 2014; Ms Anna Söderlund, Vivoline Medical AB, July 2014; and Mr Paul Henderson, NuTH, September 2014), there are several pieces of equipment and consumables needed during the EVLP procedure. The main equipment needed is a Vivoline system, which is the 'rig' unit, and a Vivoline disposable lung set, in which the lung is inserted in order to be reconditioned before the transplant. Other surgical equipment is also needed for the procedure (e.g. tissue forceps, surgical tape and sutures), while equipment for blood gases tests (e.g. syringes for blood gases and blood gases samples) and a bronchoscope are necessary for the screening of the lung. The costs of all the equipment and consumables used during an EVLP run were collected from the official websites of the respective suppliers and the hospital or Vivoline Medical staff. Where equipment is reusable, its equivalent annual costs were estimated based on its expected life expectancy, assuming a 3.5% discount rate.[52] The equivalent annual cost was then divided by the expected annual usage to get a cost per recipient.

There are several drugs that are also administered to the lung during the EVLP procedure. These include heparin sodium and methylprednisolone, as well as insulin and THAM. The CRF (p. 34) and the NuTH clinical staff (Mr Anders Andreasson, NuTH, September 2014, personal communication) provided the details of the medications used. The unit costs of the medications were obtained from the BNF 2014 based on the doses recorded on the patients' data set.[50]

Lung transplant

The procedure followed during the lung transplant is identical for both standard donor and EVLP lung transplantation. Before lung transplant, the patient is transferred in the anaesthetic room of the operating

theatre in order to receive the necessary anaesthesia. In this room, a consultant anaesthetist and an anaesthetic nurse (band 5) are required in order to provide the anaesthetic management of the patient. As described in *Post-operative care*, the anaesthetic staff move to the surgical room afterwards in order to oversee the level of anaesthesia of the patient during the operation. The anaesthetic preparation needs 45 minutes, on average, in order to be completed based on the NuTH transplant co-ordinators (Ms Alison Davison, NuTH, June 2015, personal communication). As before, the cost of the anaesthetic room, as well as the operating theatre in general, was obtained from *ISD Scotland Theatre Services,*[53] while the costs of the staff were collected from the PSSRU's *Unit Costs of Health and Social Care 2014*.[51]

Once the anaesthetic preparation is finished, the patient is moved from the anaesthetic room into the operating theatre. In addition to the anaesthetic staff (with the addition of an anaesthetic fellow), a consultant surgeon, a surgical fellow, two scrub nurses (bands 5 and 7) and a perfusionist (band 7) are required for the surgery (personal communications: A Fisher, NuTH, November 2015; and Mr Paul Henderson, NuTH, September 2014). Depending on whether a single or a double lung is transplanted, the surgery might last, on average, 4–7 hours. More information regarding the staff members needed was provided by the hospital staff that took part in the study [Qualtrics® survey, 2014 (Qualtrics, Provo, UT, USA); see *Appendix 5*], while their costs per hour were calculated from the PSSRU's *Unit Costs of Health and Social Care 2014*.[51]

As far as the equipment and consumables used during lung transplant are concerned, during the analysis of this study, it was difficult to obtain more details from the different members of the hospital staff and conduct the relevant microcosting. As a result, this information was omitted from the estimation of costs.

Post-operative care

After the operation is completed, the lung recipient is initially transferred to the ITU in order to be closely observed by the anaesthetic team and the transplant physicians. On average, the patient stays for 10 days in the ITU/high-dependency unit (HDU) before being discharged to the transplant ward. After being discharged from the ITU/HDU, some recipients might require to stay for longer (> 1 month, on average) in the hospital so they remain at the level 1 ward. Others might experience complications and may need to be readmitted to ITU/HDU. The time spent in the different hospital wards after the operation was reported on the CRF of the study. The unit costs of the wards were measured per bed-day and were calculated in accordance with the *NHS Reference Costs 2013/2014*.[49] The costs of the wards included the costs of the ward, equipment and nursing needed during the patient's hospital stay.

In the ITU/HDU, the patient is observed daily by a consultant surgeon (15 minutes), a surgical fellow (15 minutes), a consultant physician (10 minutes), a consultant anaesthetist (30 minutes) and an anaesthetic fellow (90 minutes). In the hospital ward, there are no visits from the consultant surgeon, the consultant anaesthetist and the anaesthetic fellow, but the consultant physician time increases to 20 minutes, and a transplant specialist registrar is now needed, who will spend approximately 30–40 minutes with each patient every day. During their visits, the clinicians perform several diagnostic tests in order to monitor the progress of the patient's health (e.g. ABG, FBC, lung function test, etc.). Depending on the patient's condition, a tracheostomy and a bronchoscopy may be required. The CRF gave more details regarding the use of these tests and procedures, while the staff time needed per day was estimated based on the responses of the clinicians on the Qualtrics survey (see *Appendix 5*). The costs per hour for all the members of the staff were collected from the PSSRU's *Unit Costs of Health and Social Care 2014*,[51] while the unit costs of the tests and procedures performed were calculated using the NuTH costing tool (obtained from www.newcastlejro.org.uk) or *NHS Reference Costs 2013/2014*.[49]

During post-operative care, some patients might require both cardiac and respiratory support if their heart and/or lungs are unable to provide adequate amount of gas exchange to sustain life. This can be solved by using either an ECMO machine, which artificially removes carbon dioxide from the person's blood and oxygenates red blood cells, or an iLA device, which is an artificial membrane that replaces the lung and its functions. In addition, normally haemodynamic support is provided to the patient by using inotrope drugs

(e.g. adrenaline hydrochloride, vasopressin, dobutamine, etc.). In some cases, some plasma volume expanders, such as colloid (e.g. normal saline solution) and crystalloid (e.g. albumin, dextran, etc.) fluids, might be required in order to restore the vascular volume and stabilise the circulatory haemodynamics. When needed, red blood cells, plasma and platelets might also be given in order to change the levels of the main blood components.

The use and amount of all the equipment and consumables described above were recorded on the patient's CRF (p. 45), while their costs were retrieved from different sources. The costs of ECMO and the blood components were given by the hospital staff (personal communications: Mr Tanveer Butt, NuTH, September 2014; and, Mr Paul Henderson and Ms Yvonne Scott, NuTH, July 2015) or the NHSBT. Using the same methods as described before for reusable equipment (e.g. ECMO machine) a cost per recipient was calculated.[52] The unit costs of colloid and crystalloid fluids, as well as that of the inotrope drugs used, were collected from the BNF.[50]

As mentioned above, the patient might be readmitted to ITU/HDU or hospital if any serious complications develop after the operation. The type of management provided is linked to the type of complication experienced. The CRF (pp. 52–58) gave all the information on the type of complications and management received. The unit costs of the procedures came from the *NHS Reference Costs 2013/2014,*[49] whereas all the medications given as a result of rejection or infection episodes were obtained from the BNF.[50]

Outpatient care

According to the recommendations of the hospital staff, a lung recipient will need to visit the transplant clinic every few weeks or months in the first year after the operation. During every outpatient visit, the patient is seen for half an hour by a consultant physician and a clinic nurse (band 5). The clinic staff also arrange a FBC, a urea and electrolytes and a liver function test, chest radiography, a pulmonary function test and a bronchoscopy at 1, 3, 6 and 12 months, routinely or at other times if indicated by the recipients' condition. The information about the use of the tests provided was reported on the CRF, while the outpatient hospital staff gave more information regarding the time spent with the patient (Ms Lyndsey Forrest, NuTH, September 2014, personal communication). The costs of the tests were calculated using the NuTH costing tool (obtained from: www.newcastlejro.org.uk) or the *NHS Reference Costs 2013/2014*,[49] whereas the cost of the staff was measured per hour based on the PSSRU's *Unit Costs of Health and Social Care 2014*.[51]

Immunosuppressive medications are prescribed from immediately after the transplant operation and are dispensed when a lung recipient is discharged from the hospital in order to reduce the risk of rejection of the donor lungs. If the patient shows any AEs, rejection or infection episodes, these can be reported either at an outpatient hospital and GP visit, where a clinical diagnosis/biopsy is performed, or the patient can call the transplant centre for further advice. Depending on the complications reported, there might be some new medications or current treatment may be changed. In some cases, a readmission to the ITU/HDU or the level 1 hospital ward might be required. Information on changes in medications was included on the CRF for every outpatient visit. The costs of the diagnostic and treatment procedures provided by the hospital were collected from the *NHS Reference Costs 2013/2014,*[49] whereas the unit costs of the medications were obtained from the BNF.[50] For the GP visits, the costs were calculated per hour based on the costs of the GP per hour from the PSSRU's *Unit Costs of Health and Social Care 2014*.[51]

Concomitant medications

There were some additional medications given to the lung recipients depending on their health condition while the study was under way. As it is always difficult to define whether these drugs are required as a result of the transplant or because of other medical conditions, they were reported and costed separately. The doses and duration of treatment for these medications were defined by the CRF of the study or the BNF[50] in case the information was missing. The BNF[50] was also used in order to provide the unit costs of the concomitant medications used throughout the study.

Cost data analysis

As described previously, the cost analysis of the study data was divided in eight different stages (e.g. donor's hospital, lung retrieval, etc.) based on the sequence of events of each one of the two transplant procedures that were examined. Each stage was also subdivided into groups in accordance with the point of time that the respective resources were used (e.g. initial assessment, tests, staff time, etc.). The unit costs of each resource were obtained from different sources (e.g. BNF,[50] PSSRU[51]) and they were then multiplied by the mean usage of each resource as reported on the CRF or from the hospital staff (see *Appendices 6* and *7*). The total costs of each resource were added in order to give the total cost of each group of resources, which were further added in order to provide the total cost of each stage of the transplant process. At the end, the total cost of the transplant was calculated for each lung recipient, and the average cost per recipient was estimated. As noted above, in order to cost the two transplant procedures, a bottom-up methodology was used instead of using the *Reference Costs 2013/2014*[49] for lung transplantation. This is because the EVLP procedure is a new procedure and so not adequately captured in routine data sources. It is also essential to mention that for the EVLP arm of the study, the resource costs of the first four stages (i.e. donor's hospital, lung retrieval, transplant preparation and EVLP procedure) were multiplied by 53/18 in order to consider the additional costs of the lungs that were retrieved and not transplanted for each EVLP recipient. In other words, for every 2.9 set of lungs retrieved only one transplant was performed. Therefore, the cost of a transplant included the cost of the 2.9 retrievals.

The mean and median costs per recipient for each stage of each one of the two transplant procedures are presented together with the relevant SD and IQR (see *Tables 30–37*). All costs are rounded to their nearest pound sterling. Although this is a descriptive analysis with no intention to directly compare the two transplant procedures in terms of their costs, the mean difference in cost per recipient – with its standard error – is indicated in each table (the minus symbol in the mean difference in cost per recipient between the two arms of the study indicates that the mean cost of the respective resources is lower in the standard donor arm than in the EVLP lung transplant arm). A 95% CI of the mean difference in the cost of the two procedures per recipient is also estimated based on statistical bootstrapping of the available data, which is used to simulate a CI and is useful when data are not parametrically distributed and conventional (parametric) statistical approaches may be inappropriate. Both mean cost differences and 95% CIs are presented for descriptive purposes, with no intention to directly compare the two transplant procedures. The analysis of the costs of the study was conducted using the statistical and decision analysis software Stata 13.1.

Quality of life

In order to examine the changes in HRQoL for each patient, QALYs were measured using the participant responses on the SF-36[54] questionnaire administered at the start of the study (baseline), when the participant was added into the waiting list, 90 days and 12 months after lung transplant. In order to measure QALYs, participant responses were then mapped onto the SF-6D using a validated algorithm[48] to determine utility values. These utility values had a range from 0 (death) to 1 (perfect health), with the utility value of lung transplant ranking within these two boundaries. The SF-6D score was taken as 0 from the date of death to the end of follow-up, the date of death was recorded as part of the data collection. QALYs were then to be estimated for each study participant using the trapezoid rule. The SF-36 was preferred in this context, as it was felt to be more sensitive over the range of likely health states experienced by an individual than alternative preference-based quality-of-life tools.

Health outcome data analysis

The low rate of questionnaire completion at each stage of the study (see *Table 22*) meant that assumptions needed to be made in order to follow the procedure described in *Cost and use of resources*, and this would limit the robustness and increase the bias of the results. Methods, such as multiple imputation, would be useful in these cases; however, given the limited overall sample size and the quality of missing data, it was felt that imputed data might be potentially misleading. For this reason, it was decided that the mean (SD) and median (IQR) SF-6D scores would be calculated for each data collection time point (i.e. baseline, 3 and 12 months post transplant) based on the number of observations (*n*) available at those time points. The means were then used as point estimates in order to measure the area

under the curve, using the trapezoid rule, to give the mean QALYs per transplant type. As in the analysis of costs, no direct comparison between the total numbers of QALYs for each transplant procedure was conducted. This was, again, because of the limited number of data available. The analysis of the SF-36 data of the study was conducted using Stata 13.1.

Net benefits

Based on the values of total costs and QALYs that were measured from the standard donor and EVLP lung transplants, the net benefit of each one of the two procedures was proposed to be calculated using the following equation:

$$\text{Net benefit} = \text{QALY} \times \lambda - \text{cost}, \quad (1)$$

where λ is the current NHS cost-effectiveness threshold (£20,000 per QALY).[52] However, owing to the limitations of the quality-of-life data, which were mentioned above, the calculation of the study net benefits was not performed, as it would not produce any accurate or meaningful results.

Missing data

As already mentioned, the data available for comparative purposes were very limited, and there were missing data for study participants. Therefore, the nature and extent of missing data were reported, and no imputation was attempted. The exceptions to this were that if the missing data were related to standard resources that are normally used during the treatment pathway, it was assumed that these resources were used and, therefore, costs were added.

Results

Cost analysis

The total average cost per recipient, by each area of resource use for each one of the eight stages of the study, is listed in *Economic evaluation methods* (see *Tables 30–37*).

Table 30 shows that there were no large variations in the costs of the screening and testing of the donor before the lung retrieval in either of the two types of transplantation. This is because the hospital staff always perform the same type and number of tests in order to examine the person's health condition before requesting a retrieval team to arrive at the hospital. Any small variations observed in the donor's initial assessment costs (standard transplant, SD £6; EVLP transplant, SD £18) might be caused by the fact that some of the tests might not be needed in some cases or had been provided recently to the donor. In this stage, medication costs constitute a small component of the total costs, as only methylprednisolone was given as a single dose, whereas the main component of costs for both standard and EVLP lung transplants are the diagnostic tests. In addition, the large differences in mean costs between the two transplant procedures ($\text{Cost}_{\text{STD}} = £403$; $\text{Cost}_{\text{EVLP}} = £1182$) are because in the EVLP arm only 18 lungs were transplanted out of 53 that were retrieved, while in the standard arm all retrieved lungs were transplanted.

The retrieval of the lung involves very similar resources regardless of the subsequent procedure. As can be seen from *Table 31*, there is some variability in the costs of the equipment used for a DCD and a DBD donor. This is because, during a DBD, the heart is still working and, therefore, an ABG test can also be performed. This also explains the small differences observed in the cost of the tests provided by the retrieval team (standard, SD £9; EVLP, SD £36). Moreover, some variation is observed in the cost of the lung perfusion. This might mean that some of the medications that are normally used during the perfusion of the organ were not needed in practice or that there were several missing patient data items that caused these differences in costs. In this stage, the main components of costs are the staff time and the team's travelling costs, which would be expected given the potential distances that the scout and retrieval teams have to travel and the time needed to complete the organ retrieval. As mentioned before, the large increase in the costs of the EVLP compared with the standard transplant was mainly caused by the different retrieval-to-transplant ratio of the two transplant procedures.

TABLE 30 Total average cost per recipient by each area of resource use: donor's hospital total average cost per recipient

		Study group				Mean (SE) difference in cost per recipient	95% CI based on bootstrapping
		Standard ($n = 184$)		EVLP ($n = 18$)			
Resource use	Patient details	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)		
Total initial assessment costs	Donor	£392 (£6)	£393 (£391–395)	£1156 (£18)	£1163 (£1151–1163)	–£765 (£2)	
Total drug costs	Donor	£11 (£10)	£17 (£0–17)	£26 (£26)	£26 (£0–51)	–£14 (£3)	
Total donor's hospital costs	Donor	£403 (£12)	£408 (£395–412)	£1182 (£35)	£1182 (£1163–1214)	–£779 (£4)	–£786 to –£771

SE, standard error.

TABLE 31 Total average cost per recipient by each area of resource use: lung retrieval total average cost per recipient

		Study group				Mean (SE) difference in cost per recipient	95% CI based on bootstrapping
		Standard ($n = 184$)		EVLP ($n = 18$)			
Resource use	Patient details	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)		
Total DCD donor equipment costs	Donor	£25 (£4)	£21 (£21–29)	£63 (£0)	£63 (£63–63)	–£38 (£2)	
		$n = 30$		$n = 4$			
Total DBD donor equipment costs	Donor	£273 (£3)	£274 (£274–274)	£799 (£11)	£806 (£782–806)	–£527 (£1)	
		$n = 154$		$n = 14$			
Total staff time costs	Donor	£1005 (£0)	£1005 (£1005–1005)	£2958 (£0)	£2958 (£2958–2958)	–£1954 (£0)	
Total test costs	Donor	£21 (£9)	£25 (£25–25)	£49 (£36)	£74 (£0–74)	–£28 (£3)	
Total perfusion costs	Donor	£623 (£142)	£655 (£655–655)	£1822 (£455)	£1929 (£1929–1929)	–£1199 (£47)	
Total travelling costs	Donor	£6770 (£0)	£6770 (£6770–6770)	£19,934 (£0)	£19,934 (£19,934–19,934)	–£13,164 (£0)	
Total lung retrieval costs	Donor	£8651 (£170)	£8729 (£8695–8729)	£25,398 (£524)	£25,688 (£24,957–25,700)	–£16,747 (£55)	–£16,856 to –£16,639

SE, standard error.

Table 32 describes the costs of the preparation of the patient before lung transplant. As with the previous two stages of the analysis, there is some variation in the use of the screening tests performed, which might mean either that the test was performed but these data were missing, or that or no test was required during the preparation of the patient. The table also indicates that the most costly resource used during this stage of the transplant process was the time spent in the hospital ward before surgery (£265 per hour). Obviously, the retrieval-to-transplant EVLP ratio (53/18) results in the higher costs for the EVLP arm of the study. Furthermore, as mentioned above in the description of the lung transplant procedure, in this study it was difficult to obtain detailed information about the resources used for the patient transportation to the transplant site. As a result, these costs are missing from *Table 31*. Given the difference in retrieval-to-transplant ratios between the two arms of the study and the nature of these costs, it might be expected that the costs of travelling would increase the cost of the patient preparation and, subsequently, the cost of the total transplant procedure.

Table 33 describes the costs for the EVLP procedure. Obviously, because the EVLP procedure is performed only during EVLP lung transplant, no costs are presented for the standard arm of the study. This process includes the assessment and reconditioning of the lung in order to make it suitable for transplant, and it is a stage that occurs between the transplant preparation and the transplant surgery. As expected, the most costly resources used in this stage are the consumables needed for the procedure. These include the lung set in which the lung is reconditioned (Vivoline disposable lung set, £6963). The medications used for the reconditioning of the organ add to the costs of the procedure, as do the cost of staff time and theatre time, because the EVLP procedure lasts for approximately 6 hours. As described in the stages above, the retrieval-to-transplant ratio causes an additional increase in the costs of the EVLP procedure by 53/18.

The cost of the single lung transplant procedure or a double lung transplant procedure does not vary according to whether it is a standard or EVLP lung transplantation. In this study, only 26 transplants were reported as single, of which two were in the EVLP arm. The rest of the transplants were either reported as double or assumed to be double in this analysis given that more double transplants were performed. A double lung transplant increases the time needed for the surgery by approximately 3 hours, which leads to a significant increase in the mean transplant costs (single transplant cost £4177; double transplant cost £6934), because of increased theatre usage and staff time costs. The variability within the total costs of the transplant (standard, SD £931; EVLP, SD £892) is mainly caused by the difference in the proportion of single or double lung transplants performed in the standard and EVLP arms of the study. As indicated in *Table 34*, the total cost of the equipment/consumables used during the operation is missing. This is because every surgeon and clinic may differ in how the surgery is performed and, hence, may use different equipment. In this study it was difficult to collect more details about the resources used in order to retrieve their respective costs.

The post-operative and outpatient care of the patients shows the largest variability in total costs (see *Tables 35* and *36*) because it is dictated by the nature and severity of any complications and AEs that might occur, which vary markedly between patients. Given the nature of events that might occur and the cost of their management, it would be expected that these costs would be highly skewed, and the mean cost, especially for the EVLP arm, would be greatly affected by the very high costs incurred by a small number of patients. As indicated in *Table 35*, the highest costs in this stage are the ward use (standard arm, £20,064; EVLP arm, £21,276) and staff time costs (standard arm, £4828; EVLP arm, £5265). This is because the length of hospital stay (especially in the ITU/HDU) varies between different patients and, consequently, different amounts of staff time are required. *Table 35* also shows a large variation in the costs of the equipment used. In this case, the variation is mainly caused by the use of the ECMO machine (ECMO cost, £34,000). In addition, variation is also observed in the costs caused by complications and infection episodes. This is to be expected given the fact that each recipient responds differently to their transplanted organ, and thus some patients become more prone to infections than others. (It should be mentioned that the infection episodes and airway complication costs presented in *Table 35* include the costs from infections that occur either straight after the transplant or during the subsequent outpatient care of the patient.)

TABLE 32 Total average cost per recipient by each area of resource use: transplant preparation total average cost per recipient

Resource use	Patient details	Study group				Mean (SE) difference in cost per recipient	95% CI based on bootstrapping
		Standard ($n = 184$)		EVLP ($n = 18$)			
		Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)		
Total potential recipient contacting costs	Recipient	£30 (£0)	£30 (£30–30)	£90 (£0)	£90 (£90–90)	–£59 (£0)	
Total potential recipient meeting costs	Recipient	£61 (£0)	£61 (£61–61)	£179 (£0)	£179 (£179–179)	–£118 (£0)	
Total tissue typing costs	Recipient	£60 (£0)	£60 (£60–60)	£176 (£0)	£176 (£176–176)	–£116 (0)	
Total test costs	Recipient	£50 (£8)	£51 (£51–55)	£140 (£28)	£149 (£149–149)	–£90 (£3)	
Total ward time costs	Recipient	£265 (£0)	£265 (£265–265)	£780 (£0)	£780 (£780–780)	–£515 (£0)	
Total drug costs	Recipient	£0 (£0)	£0 (£0)	£0 (£0)	£0 (£0)	£0 (£0)	
Total transfer to ward costs	Recipient	Missing	Missing	Missing	Missing	Missing	
Total transplant preparation costs	Recipient	£466 (£8)	£467 (£467–471)	£1365 (£28)	£1375 (£1375–1375)	–£899 (£3)	–£905 to –£894

SE, standard error.

TABLE 33 Total average cost per recipient by each area of resource use: EVLP procedure total average cost per recipient

Resource use	Patient details	Study group				Mean (SE) difference in cost per recipient	95% CI based on bootstrapping
		Standard ($n = 184$)		EVLP ($n = 18$)			
		Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)		
Total staff time costs	EVLP recipient	–	–	£1533 (£0)	£1533 (£1533–1533)		
Total equipment costs	EVLP recipient	–	–	£59 (£0)	£59 (£59–59)		
Total consumable costs	EVLP recipient	–	–	£22,958 (£606)	£23,017 (£22,487–23,193)		
Total miscellaneous equipment costs	EVLP recipient	–	–	£220 (£0)	£220 (£220–220)		
Total theatre usage costs	EVLP recipient	–	–	£10,382 (£0)	£10,382 (£10,382–10,382)		
Total drug costs	EVLP recipient	–	–	£7482 (£1965)	£7991 (£6362–8057)		
Total EVLP procedure costs	EVLP recipient	–	–	£42,633 (£2172)	£42,675 (£41,167–43,414)	–	–

SE, standard error.

TABLE 34 Total average cost per recipient by each area of resource use: lung transplant total average cost per recipient

Resource use	Patient details	Study group				Mean (SE) difference in cost per recipient	95% CI based on bootstrapping
		Standard ($n = 184$)		EVLP ($n = 18$)			
		Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)		
Total anaesthetic preparation costs	Recipient	£501 (£0)	£501 (£501–501)	£501 (£0)	£501 (£501–501)	£0 (£0)	
Total single lung surgery staff time costs	Recipient	£1325 (£0)	£1325 (£1325–1325)	£1325 (£0)	£1325 (£1325–1325)	£0 (£0)	
		$n = 24$		$n = 2$			
Total double lung surgery staff time costs	Recipient	£2320 (£0)	£2320 (£2320–2320)	£2320 (£0)	£2320 (£2320–2320)	£0 (£0)	
		$n = 160$		$n = 16$			
Total single lung surgery theatre usage costs	Recipient	£2351 (£0)	£2351 (£2351–2351)	£2351 (£0)	£2351 (£2351–2351)	£0 (£0)	
		$n = 24$		$n = 2$			
Total double lung surgery theatre usage costs	Recipient	£4114 (£0)	£4114 (£4114–4114)	£4114 (£0)	£4114 (£4114–4114)	£0 (£0)	
		$n = 160$		$n = 16$			
Total equipment/consumable costs	Recipient	Missing	Missing	Missing	Missing	Missing	
Total single transplant costs	Recipient	£4177 (£0)	£4177 (£4177–4177)	£4177 (£0)	£4177 (£4177–4177)	£0 (£0)	
		$n = 24$		$n = 2$			
Total double transplant costs	Recipient	£6934 (£0)	£6934 (£6934–6934)	£6934 (£0)	£6934 (£6934–6934)	£0 (£0)	
		$n = 160$		$n = 16$			
Total lung transplant costs	Recipient	£6574 (£931)	£6934 (£6934–6934)	£6627 (£892)	£6934 (£6934–6934)	–£53 (£229)	–£505 to £399

SE, standard error.

TABLE 35 Total average cost per recipient by each area of resource use: post-operative care total average cost per recipient

		Study group				Mean (SE) difference in cost per recipient	95% CI based on bootstrapping
		Standard ($n = 184$)		EVLP ($n = 18$)			
Resource use	Patient details	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)		
Total staff time costs	Recipient	£4828 (£5331)	£2895 (£1721–6059)	£5265 (£5065)	£2741 (£1996–7795)	–£436 (£1311)	
Total test costs	Recipient	£135 (£77)	£183 (£14–183)	£115 (£87)	£183 (£14–183)	£19 (£19)	
Total ward usage costs	Recipient	£20,064 (£20,582)	£12,143 (£7459–25,453)	£21,276 (£23,651)	£11,605 (£5944–28,700)	–£1212 (£5152)	
Total procedure costs	Recipient	£158 (£167)	£135 (£0–340)	£336 (£150)	£340 (£340–475)	–£178 (£41)	
Total equipment costs	Recipient	£3696 (£13,726)	£0 (£0–0)	£22,667 (£30,855)	£0 (£0–68,000)	–£18,971 (£3931)	
Total consumable costs	Recipient	£826 (£1711)	£453 (£164–791)	£1469 (£3009)	£708 (£360–1320)	–£644 (£459)	
Total inotrope costs	Recipient	£16 (£15)	£10 (£4–27)	£22 (£17)	£23 (£4–34)	–£6 (£4)	
Total post-implantation haemodynamic support costs	Recipient	£43 (£160)	£2 (0–14)	£278 (£437)	£120 (£8–224)	–£235 (£49)	
Total complication costs	Recipient	£699 (£1799)	£0 (0–70)	£2246 (£2973)	£0 (£0–4580)	–£1547 (£476)	
Total airway complication costs	Recipient	£622 (£2020)	£0 (£0–0)	£0 (£0–0)	£0 (£0–0)	£622 (£477)	
Total ITU rejection episode costs	Recipient	£59 (£224)	£0 (£0–0)	95 (275)	£0 (£0–0)	–£36 (£57)	
Total ward rejection episode costs	Recipient	£242 (£452)	£0 (£0–851)	198 (381)	£0 (£0–0)	£45 (£110)	
Total infection episode costs	Recipient	£3925 (£14,046)	£286 (£0–1755)	£3518 (£7830)	£39 (£0–1738)	£407 (£3366)	
Total post-operative care costs	Recipient	£34,109 (£39,561)	£20,112 (£11,639–42,340)	£56,136 (£57,345)	£21,931 (£12,713–86,464)	–£22,027 (£10,217)	–£42,174 to –£1879

SE, standard error.

The data in *Table 36* demonstrate that the outpatient care of a lung recipient varies markedly between participants. Some patients might require more outpatient or GP visits, whereas others might need several unplanned hospital admissions and longer duration of treatment with immunosuppressive medications. The last two resources constitute almost the 70% of the outpatient care costs. As expected, the unplanned hospital admissions of the recipients show a large variation, as their occurrence varies between different patients.

Concomitant medications can be considered as an additional part of the analysis of this study. A recipient might need an additional treatment or a change in the current treatment as a result of complications. The duration of treatment is also variable and depends on the condition of the patient. Therefore, the medications given vary between patients, and this explains why such a large variation in the total cost of concomitant medications exists (standard, SD £4505; EVLP, SD £3614) in *Table 37*.

Table 38 presents the total average cost per recipient for the standard donor and the EVLP lung transplantation. These costs were calculated by adding the total costs of each stage of the transplant procedure for each patient and calculating the average cost for each lung recipient. As can be seen from *Table 38*, the mean and median cost of EVLP per recipient is substantially greater than for standard lung transplant. This is partially because of the different retrieval-to-transplant ratio between the two lung transplants, which leads to higher costs in the early stages of the analysis and, partially, as a result of the actual cost of the EVLP procedure (£14,479 per lung assessed). Also presented in *Table 38* is the mean difference and bootstrapped 95% CI. The CI suggests that EVLP recipients are, on average, at least £57,910 more costly and may be as much as £101,036. These data are only suggestive given the very small number of participants in the EVLP arm ($n = 18$).

In *Figure 21*, the costs of each stage of both standard and EVLP lung transplant procedures are presented as a bar chart. This reveals the significant difference in costs for certain parts of the procedure pathways between standard and EVLP transplants.

Analysis of the quality of life

As indicated in *Table 39*, there were only a small number of lung recipients who contributed SF-6D data (22/202) at all expected time points. These patients were those who completed the SF-36 questionnaire at all three time points, or were known to have died by a given time point, in which case SF-6D scores for that and any subsequent time points were given as zero. As a result, *Table 40* presents the mean and median SF-6D utility scores for each stage that a questionnaire was completed or a patient was reported as being dead (i.e. at baseline, 3 and 12 months post transplant). It also presents the number of observations (n) based on which the means and the medians were calculated at each time point. At the bottom of the table, the total mean QALYs of each transplant type are shown, which were estimated by measuring the area under the curve created from the mean utility scores of each one of the three time points.

Figure 22 presents the differences between the mean SF-6D scores between the two lung transplant procedures. As was expected from the numbers provided in *Table 40*, the differences are negligible. However, because these are the mean SF-6D scores reported, a comparison between the numbers of QALYs gained from each one of the two procedures would be meaningless.

Predicting NHS expenditure costs for UK patients receiving a lung transplant: a regression-based analysis

Rationale

The aim of this part of the economic analysis was to identify the key determinants of costs to the NHS of a lung transplant. This aim was met by using information and data collected from the DEVELOP-UK study in a regression model, where the dependent variable was the NHS costs for a lung transplant and the independent (explanatory) variables were potential determinants of these costs. The purpose of the analysis

TABLE 36 Total average cost per recipient by each area of resource use: outpatient care total average cost per recipient

Resource use	Patient details	Study group				Mean (SE) difference in cost per recipient	95% CI based on bootstrapping
		Standard ($n = 184$)		EVLP ($n = 18$)			
		Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)		
Total outpatient review costs	Recipient	£1420 (£699)	£1515 (£895–2170)	£994 (£842)	£766 (£209–1855)	£426 (£176)	
Total staff time costs	Recipient	£130 (£50)	£159 (£120–159)	£100 (£70)	£139 (£40–159)	£31 (£13)	
Total rejection episode costs	Recipient	£750 (£3443)	£0 (0–653)	£290 (£463)	£0 (£0–379)	£460 (£814)	
Total GP visit costs	Recipient	£9 (£22)	£0 (£0–0)	£18 (£29)	£0 (£0–34)	–£9 (£6)	
Total unplanned hospital admission costs	Recipient	£2748 (£10,864)	£0 (£0–559)	£689 (£2395)	£0 (£0–392)	£2059 (£2572)	
Total immunosuppressive medication costs	Recipient	£2923 (£1049)	£3187 (£2680–3522)	£2475 (£1522)	£3222 (£1003–3475)	£447 (£271)	
Total outpatient care costs	Recipient	£7981 (£12,263)	£5746 (£4552–7025)	£4567 (£3931)	£4969 (£1423–5805)	£3414 (£2911)	–£2326 to £9153

SE, standard error.

TABLE 37 Total average cost per recipient by each area of resource use: concomitant medication total average cost per recipient

Resource use	Patient details	Study group				Mean (SE) difference in cost per recipient	95% CI based on bootstrapping
		Standard ($n = 184$)		EVLP ($n = 18$)			
		Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)		
Total concomitant medication costs	Recipient	£1424 (£4505)	£0 (£0–328)	£1172 (£3614)	£0 (£0–0)	£252 (£1096)	–£1908 to £2412

SE, standard error.

TABLE 38 Total average cost per recipient per procedure

Resource use	Patient details	Study group: Standard ($n = 184$) Mean (SD)	Standard ($n = 184$) Median (IQR)	EVLP ($n = 18$) Mean (SD)	EVLP ($n = 18$) Median (IQR)	Mean (SE) difference in cost per recipient	95% CI based on bootstrapping
Total donor's hospital costs	Donor	£403 (£12)	£408 (£395–412)	£1182 (£35)	£1182 (£1163–1214)	–£779 (£4)	–£786 to –£771
Total lung retrieval costs	Donor	£8651 (£170)	£8729 (£8695–8729)	£25,398 (£524)	£25,688 (£24,957–25,700)	–£16,747 (£55)	–£16,856 to –£16,639
Total transplant preparation costs	Recipient	£466 (£8)	£467 (£467–471)	£1365 (£28)	£1375 (£1375–1375)	–£899 (£3)	–£905 to –£894
Total EVLP procedure costs	EVLP recipient	–	–	£42,633 (£2172)	£42,675 (£41,167–43,414)	–	–
Total lung transplant costs	Recipient	£6574 (£931)	£6934 (£6934–6934)	£6627 (£892)	£6934 (£6934–6934)	–£53 (£229)	–£505 to £399
Total post-operative care costs	Recipient	£34,109 (£39,561)	£20,112 (£11,639–42,340)	£56,136 (£57,345)	£21,931 (£12,713–86,464)	–£22,027 (£10,217)	–£42,174 to –£1879
Total outpatient care costs	Recipient	£7981 (£12,263)	£5746 (£4552–7025)	£4567 (£3931)	£4969 (£1423–5805)	£3414 (£2911)	–£2326 to £9153
Total concomitant medication costs	Recipient	£1424 (£4505)	£0 (£0–328)	£1172 (£3614)	£0 (£0–0)	£252 (£1096)	–£1908 to £2412
Total cost per procedure	–	£59,608 (£42,664)	£43,630 (£33,833–68,748)	£139,081 (£58,916)	£108,255 (£93,492–171,768)	–£79,473 (£10,935)	–£101,036 to –£57,910

SE, standard error.

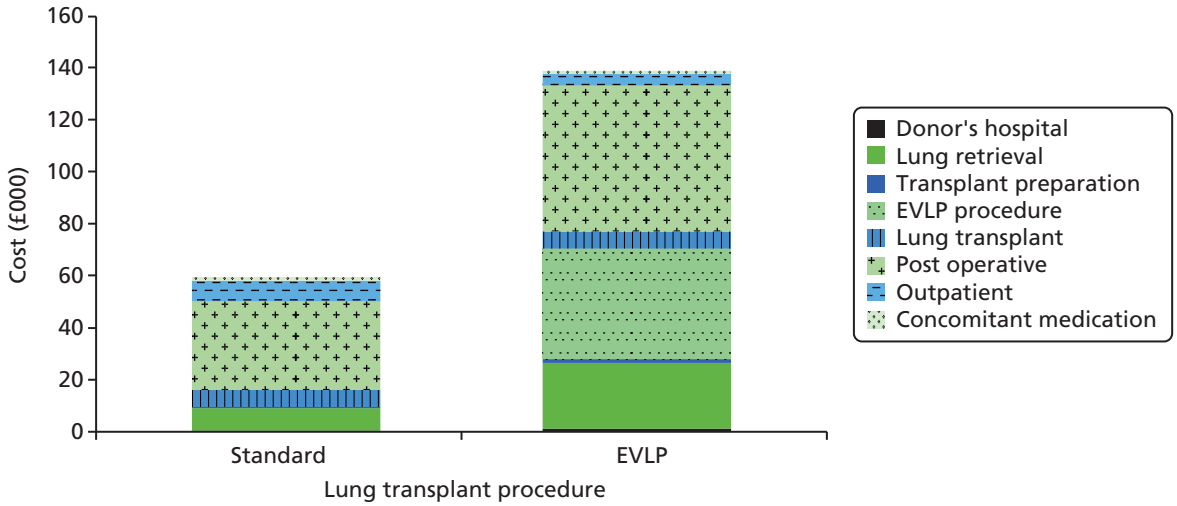

FIGURE 21 Total average cost per recipient per procedure.

TABLE 39 Percentage of SF-6D data available for each arm and stage of the study

Study group	Time point						
	Baseline only, % (*n*)	3 months only, % (*n*)	12 months only	Baseline and 3 months, % (*n*)	Baseline and 12 months, % (*n*)	3 and 12 months, % (*n*)	Baseline, 3 and 12 months, % (*n*)
Standard (*N* = 184)	36.41 (67)	33.15 (61)	41.30 (76)	17.94 (33)	18.48 (34)	23.37 (43)	11.41 (21)
EVLP (*N* = 18)	44.44 (8)	55.56 (10)	55.56 (10)	22.22 (4)	16.67 (3)	38.89 (7)	5.56 (1)
Total (*N* = 202)	37.13 (75)	35.15 (71)	42.57 (86)	18.32 (37)	18.32 (37)	24.75 (50)	10.89 (22)

TABLE 40 Health-related quality of life (QALYs): SF-6D scores

Questionnaires	Study group			
	Standard (*n* = 184)		EVLP (*n* = 18)	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
At baseline	0.5510 (0.0846)	0.5450 (0.5010–0.5970)	0.5880 (0.0382)	0.6000 (0.5590–0.6125)
Number of observations	67		8	
3 months post-transplant	0.5884 (0.2766)	0.6660 (0.5540–0.7570)	0.5551 (0.3942)	0.7345 (0.0000–0.7990)
Number of observations	61		10	
12 months post-transplant	0.4527 (0.3709)	0.6125 (0.0000–0.7550)	0.4689 (0.4267)	0.6010 (0.0000–0.8410)
Number of observations	76		10	
QALYs (from SF-6D mean scores)[a]	0.5328		0.5269	

a The QALYs presented in this table were calculated from the area under the curve created by the mean SF-6D scores of each time point by using the trapezoid rule.

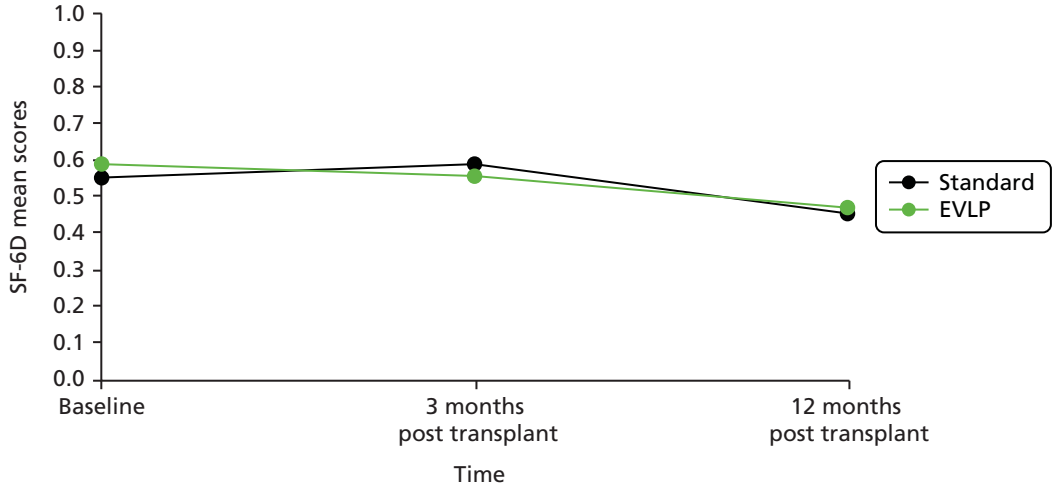

FIGURE 22 Health-related quality of life (QALY).

was to help policy-makers understand what the main determinants of costs are, and also to provide a resource for future modelling where lung transplant is a component of the care pathway modelled.

Methods

Planning the analysis

The first step was to examine the distribution of total transplant costs estimated in order to help decide which type of statistical model would best suit the observed distribution of the data. For example, if the costs were normally distributed, then a linear regression model (ordinary least squares) could be used. On the other hand, if the costs were highly skewed, as was anticipated, a log-linear or a log-gamma generalised linear model would be needed, with the choice between the two dependent on the explanatory variables that would be selected for the model. Based on the observed distribution, the log-transformation of the total NHS costs was considered to be the most appropriate approach to handle the impact of any outlier observations on the predictions of the total expenditure.

The next step in this analysis was to identify all the explanatory variables that could potentially be included in a regression model and define a cogent reason of their selection. From this long list of variables, the most useful variables (i.e. the ones that were thought to make the most significant contribution to the total NHS costs) were selected for the model, while the rest were removed as not being adequate to explain the magnitude or direction of costs. It was expected that there would be some variables that are strongly correlated with other variables selected for the model. These variables were omitted if they provided little additional explanatory power.

After the selection of the most important likely parameters, a preliminary analysis of the relationship between each variable and the total transplant costs was conducted, and this was further illustrated by developing the corresponding scatterplots for each regressor. Once the relationship was understood, the selected variables were introduced in the model in the most appropriate form using the step-wise regression (forward selection) technique. More precisely, the most commonly used variables in this type of economic regression analysis (e.g. demographic characteristics, such as age and sex) were used in order to build a basic econometric model. Once this was done, a new potential variable was added each time in order to check if it would be statistically significant and provide a more accurate prediction of costs. In addition, this model contained a dummy variable that took values 0 or 1 depending on whether or not an EVLP procedure was performed.

Possible explanatory variables and model structure

Table 41 presents the explanatory variables that were tested in order to build the regression model, as well as the reason for their selection. These variables were based on initial assumptions about the factors that might have an impact on the total NHS cost of lung transplant and were divided into three main categories based on the information that they provided: (1) recipient characteristics, (2) donor characteristics and (3) resource use.

According to the assumptions made above, the cost model was expected to have the following form at the beginning of the analysis, but its precise form would depend on which model fitted the data and provided robust predictions of costs (i.e. would be calibrated with the observed data):

$$\text{COSTS} = \beta_0 + \beta_1\text{AGE} + \beta_2\text{SEX} + \beta_3\text{TIME} + \beta_4\text{IND} + \beta_5\text{COM} + \beta_6\text{SF-6D} + \beta_7\text{COD} + \beta_8\text{TEST} + \beta_9\text{DIST} + \beta_{10}\text{PROC} + \beta_{11}\text{LUN} + u, \quad (2)$$

where COSTS is NHS expenditure costs; AGE is the recipient age; SEX is the recipient sex; TIME is the potential recipient's time on the waiting list; IND is the transplant indication; COM is the patient's comorbidities and medications while on the waiting list; SF-6D is the SF-6D score of the patient while on the waiting list based on their response to the SF-36 questionnaire; COD is the donor's cause of death; TEST is the donor–patient tissue compatibility test; DIST is the distance between the donor's hospital and the transplant site; PROC is the type of transplant (standard or EVLP); and LUN is the number of lungs transplanted.

TABLE 41 Possible explanatory variables for the regression model

Variable number	Explanatory variable	Reason of selection
Recipient characteristics		
1	Age (> 18 years)	The age of the recipient can affect the health-care services needed. It is common that older people are more susceptible to diseases, especially chronic diseases, and might not respond well to several treatments. Apart from the fact that there might be some compatibility issues, which might be related to age, age might lead easier to GVHD. Age is always included as a variable in this type of analysis
2	Sex	There might be differences in the resources needed depending on the sex of the recipient. This is because there are several biological differences between men and women that normally lead to different health outcomes. Sex is always included as a variable in this type of analysis
3	Time on the waiting list (i.e. time between the date added on the waiting list and the date of transplant)	The time from diagnosis and inclusion in the waiting list until lung transplantation might affect the condition of the potential recipient. Obviously here, the time that is needed to find a perfect organ match for the recipient plays the most important role. However, normally the longer the patient stays on the waiting list, the worse their condition will get and, therefore, they might be more susceptible to diseases after the operation
4	Transplant indication (reason of transplant)	The reason why a lung transplant is needed is important, as this might affect the total condition of the patient as well as the body response of the recipient to the transplant. If possible, different conditions should be grouped in wider categories in order to have more robust results at the end
5	Number of other diseases (comorbidities) and medications while on the waiting list	Other diseases might have an impact on the overall health of the potential recipient, which might mean additional costs for the NHS. If possible, these conditions should be grouped in bigger categories (e.g. cardiovascular diseases) in order to generalise the values of the variable

TABLE 41 Possible explanatory variables for the regression model (*continued*)

Variable number	Explanatory variable	Reason of selection
6	SF-6D baseline scores (i.e. on entry on to the waiting list)	These scores can provide information on the HRQoL of the potential recipient while they are on the waiting list. This information could possibly capture the condition of the patient while on the waiting list, which might affect the need for additional health-care services post transplant. The only problem with the SF-6D scores in this study was that there was only a limited number of SF-36 questionnaires completed (73/202 at baseline), which might affect the accuracy of the results. In other words, the result of the analysis would be restricted to a smaller number of observations that could lead to a systematic error in the final results
Donor characteristics		
7	Cause of death or donor type (i.e. after brain or circulatory death)	The cause of the donor's death could affect the type of the transplant and may lead to a higher possibility for GVHD. A case might be that a transplant after circulatory death might be more likely to need reconditioning before being used in a surgery (i.e. EVLP). The donor's previous condition might also affect the quality of the organ donated. However, this might be difficult to capture from the available data set
8	Donor–patient compatibility test	Instead of including all the different characteristics of the donor (e.g. age, sex, tissue characteristics), which might not have a meaningful relationship to the total transplant costs, the data from the donor–patient compatibility test (perhaps tissue typing test) could be used. In other words, there might be a scale and score with how well the tissues match that may predict any AEs or GVHD
Resource use		
9	Distance between the donor's hospital and the transplant site	The distance between the donor's hospital and the transplant site can have an impact on the cost of the retrieval/scout team. In other words, a longer distance means a higher travelling cost for the retrieval team and, consequently, higher costs for the retrieval of the lung
10	Type of transplant (i.e. standard vs. EVLP)	One of the main differences between standard and EVLP lung transplant is the occurrence of the EVLP procedure before the operation. This includes several costs, such as the cost of the disposable lung set, the Steen Solution and the operating theatre usage, which increase the cost of the transplant by almost £43,000, on average. In addition, the fact that only 18 EVLP transplants were performed compared with 53 lungs that were retrieved means that there is an extra cost associated with the reconditioning of the lung in different stages of the lung transplant procedure (i.e. donor's hospital, lung retrieval, transplant preparation). The type of the transplant might also affect the post-operative and outpatient care needed. It would, therefore, be reasonable to introduce the type of the transplant in the form of a dummy variable with value 0 if standard is performed and 1 if EVLP is followed
11	Number of lungs transplanted (i.e. single or double lung surgery)	The number of lungs that are transplanted is associated with different costs during the operation. This is because the time needed for the surgery changes and as a result, the staff time and usage time of the operating theatre changes. The number of lungs needed might also affect the post-operative and outpatient care. This variable could also take the form of a dummy variable depending on whether a single or a double lung transplant is performed

GVHD, graft-versus-host disease.

This regression was planned to generate a β_0 value and beta values for all of the independent variables in the equation. β_0 would be the intersection of the regression line with the *y*-axis (intercept). This value was not expected to have a meaningful interpretation, especially if this was a negative value, because β_0 would be anticipated to represent the minimum or average cost for the NHS. The rest of the beta values would describe the direction and magnitude of the relationship between each variable and the NHS cost of transplant. A *p*-value of < 0.05 was taken as evidence of a real difference between the expected and actual impact of each variable on the total costs.

The analysis of costs was conducted using the statistical software Stata 13.1.

Results

Base-case analysis

Figure 23 shows the distribution of costs based on the DEVELOP-UK study data. As expected, the costs were highly skewed (i.e. several patients needed additional or more expensive health-care resources), which meant that a simple linear model would not give robust results. As a consequence, the total cost variable was log-transformed. This transformation had the effect of diminishing the impact of the outlier observations on the total lung transplant costs per recipient.

Table 42 presents the variables that were finally selected for the model as well as their marginal effect on arithmetic costs. As shown in *Table 42*, the regression model was a log-linear model. In other words, there was a linear (additive) relationship between each one of the explanatory variables and the log-form of the total lung transplant costs, which is reasonable when considering that the explanatory variables were mainly qualitative (e.g. age, sex) or categorical (e.g. type of transplant procedure, number of lungs transplanted). Obviously, *Table 42* presents the exponential results of this regression model (i.e. the results of the analysis in a normal arithmetic scale).

As indicated in *Table 42*, there were nine variables that were included in the model instead of the 11 that were initially considered. The reasons for this reduction are listed below. First, the condition of the patient due to comorbidities or medications taken was found to be captured by the SF-6D score of the patient while on the waiting list. Second, the data for the donor–patient compatibility test were difficult to identify, and were possibly not recorded by the transplant sites. Third, the distance between the donor's hospital and the transplant site was difficult to calculate based on the available data, and the total costs calculated in the descriptive analysis of the study were based on estimates given by the NHS staff. Finally, it was decided that rather than using the SF-6D, the SF-36 should be used with the scores reported as the two main SF-36 summary components (i.e. MCS and PCS), where MCS and PCS are reported on a 0–100 scale, with higher

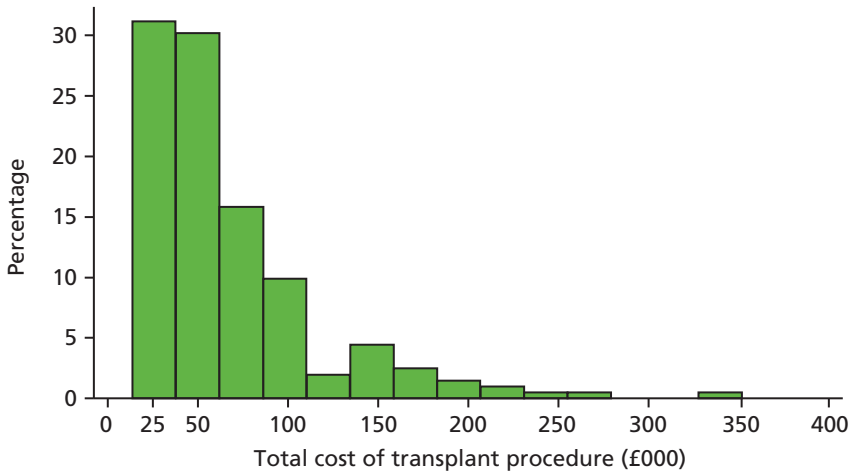

FIGURE 23 Distribution of total transplant costs based on the DEVELOP-UK study data.

TABLE 42 Explanatory variables used in the regression and their impact on total lung transplant costs

Explanatory variables	dy/dx (£)[a]	SE	z-score	$p > z$[b]	95% CI
Recipient age (years)	246	274	0.900	0.368	–290 to 782
Recipient sex (male as reference sex)					
Female	4214	5945	0.710	0.478	–7437 to 15,866
Time on the waiting list (days)	–1	9	–0.100	0.924	–19 to 17
Transplant indication (CF as reference indication)					
Non-CF bronchiectasis	36,051	24,816	1.450	0.146	–12,587 to 84,690
Interstitial lung disease	11,415	9447	1.210	0.227	–7101 to 29,931
Chronic obstructive pulmonary disease	559	7459	0.070	0.940	–14,061 to 15,179
Emphysema	–9506	7777	–1.220	0.222	–24,748 to 5736
Obliterative bronchiolitis	–11,629	9578	–1.210	0.225	–30,402 to 7144
Pulmonary hypertension	19,404	6380	3.040	**0.002**	6899 to 31,910
Other and missing indication	24,850	15,737	1.580	0.114	–5995 to 55,695
SF-36 score (MCS) while on the waiting list (score units, i.e. 0–100)	656	277	2.370	**0.018**	112 to 1199
SF-36 score (PCS) while on the waiting list (score units, i.e. 0–100)	784	372	2.110	**0.035**	56 to 1513
Donor type (DBD as reference type)					
DCD	5078	7639	0.660	0.506	–9894 to 20,050
Transplant procedure (standard transplant as reference procedure)					
EVLP	58,097	13,041	4.450	**0.000**	32,537 to 83,658
Number of lungs transplanted	30,401	10,205	2.980	0.003	10,400 to 50,403

SE, standard error.
a dy/dx is the marginal effect of the independent variable.
b When $p > z$, the probability is higher than the z-score (p-value).
Note
Values in bold represent $p < 0.05$ and are, therefore, statistically significant.

scores indicating better health, in order to have a more accurate understanding of the factors that affect the patient.

In *Table 42*, four variables are shown to be significant ($p < 0.05$) when predicting the total cost of a lung transplant for the NHS. These are the two subcomponents of the SF-36 scores ($p = 0.018$ and $p = 0.035$ for the MCS and the PCS scores, respectively), the type of the transplant procedure ($p < 0.001$) and the number of lungs transplanted ($p = 0.003$). The final two parameters were expected to be statistically significant because an EVLP transplant leads to higher costs because of the addition of the EVLP procedure before the operation ($\beta_{PROC} = 58{,}097$, which means that moving from a standard to an EVLP transplant will cost at least £58,097 more to the NHS), whereas if a double lung surgery is conducted, then more time is needed for the operation, resulting in higher staff and theatre costs. As far as the two subcomponents of the SF-36 scores are concerned, both were significant and both had a coefficient of similar magnitude ($\beta_{MCS} = 656$ and $\beta_{PCS} = 784$). This suggests that, in addition to the physical health driving lung transplant cost, the mental health of the recipient also increases the cost. Nevertheless, these effects were relatively small when compared with the total cost of transplant.

One interesting issue when looking at the impact of the SF-36 scores on the total transplant costs is the positive symbol of their coefficients. That is, the healthier a person is, the higher the costs are. There are a number of potential explanations for this. First, it could reflect the limited numbers of the SF-36 questionnaire completed at baseline (73/202 participants). This may mean that estimates derived were not very robust and were biased due to missing data, especially if those who did not complete the SF-36 were less well at baseline. Second, and related to the first reason, recipients that had lower scores were more likely to die or had a shorter time to death between the 12-month follow-up of the study than patients with higher scores, which therefore means they had less time to accrue costs. It is also interesting to mention that when the two scores were excluded from the regression model, the impact of EVLP on the total costs was higher (see *Sensitivity Analysis*).

Regarding the reason for the transplant, *Table 42* indicates that pulmonary hypertension is a predictor of cost ($p = 0.002$), whereas the rest of the indications are not. In order to examine further the significance of the indication variable and compare the different indications, an *F*-test was performed. The *F*-test is normally used when comparing two different populations of different sizes in order to examine if the variance between the two groups is bigger than the variance within each group. If the groups are significantly different, the variation in group will be bigger than the variation because of differences among individuals in each group. This test proved that the reason of transplant is a significant predictor for the model as a total ($p = 0.006$), so it would be wrong to remove it from the model, as this would lead to inaccurate coefficients for the rest of the variables of the model. Based on this test, it was also understood that there is a big difference in costs when the reason for transplant is pulmonary hypertension instead of CF, which was the reference indication during the analysis.

The demographic characteristics of the potential recipient (i.e. age and sex) seem to have a limited effect, that is, almost entirely captured by the two SF-36 subcomponent scores. This was expected since the condition of the patient, as well as the tissue compatibility between the donor and the recipient, would be the main reasons for any complications or AEs. However, age and sex should always be in this type of regression model to represent the characteristics of the patient. The same argument can be also used when examining the low impact of the donor type on the total costs. Perhaps the donor's cause of death does not influence the cost of the transplant directly, and it is the tissue compatibility that plays the most important role here. Additionally, the time on the waiting list has the smallest impact ($\beta_{TIME} = -1$) of all variables. In other words, for every additional day on the waiting list, transplant costs reduce by £1. Again, the longer the time on the waiting list the worse the condition of the patient gets and potentially the less likely they will survive to accrue costs. However, it is worth noting that the impact is very small and, although statistically significant, may not be of any practical significance.

Finally, based on the analysis of the DEVELOP-UK study data, it was calculated that the constant (β_0) of the regression model is equal to 3898. In this regression, this number is the minimum or average cost for a lung transplant for a reference participant who is male, was referred for transplant as a result of CF, received a standard single lung transplant, where the organ retrieved was from DBD. The intercept was also calculated by controlling for age, time on the waiting list and SF-36 subcomponent summary scores.

Sensitivity analysis

Given the limited number of responses to the SF-36 questionnaire, a sensitivity analysis was performed where both subscores were omitted from the model and all the observations were tested. This approach would reduce the fit of the statistical model, but would allow more of the sample available for the analysis.

The new model contained seven variables, but did not fit the data as well as the base-case analysis (R^2 was equal to 0.338 compared with 0.539 before). This suggests that the loss of model fit when using the larger data set makes the result unreliable. The transplant procedure, as well as the number of lungs that were transplanted, remained significant ($p < 0.001$ and $p = 0.004$, respectively), as was the reason for the transplant (probability > $F = 0.002$), but this time other and/or missing indications were the predictors of cost instead of the pulmonary hypertension that was in the base-case analysis.

Conclusion

In conclusion, the base-case regression model described above was the best possible model that could fit the data that were available from the DEVELOP-UK study. Based on this model, there were four variables that were significant when predicting the cost of a lung transplant for the NHS: the two components of the SF-36 scores (i.e. mental and physical component summary), the type of the transplant procedure and the number of lungs that are transplanted. Although this model can be used in further research in this area, it should be considered that it was constrained by the limited number of data from the study. Of course, the fact that this model was based on only 73 observations (owing to the small number of SF-36 questionnaires completed) further limits its robustness and estimation power. However, given the results of the sensitivity analysis that was performed where the two SF-36 summary components were omitted and where all the observations were tested, it was confirmed that the type of transplant and the number of lungs remain significant when trying to predict the total transplant costs for the NHS. Furthermore, the fact that it was not possible to collect the data from the donor–patient tissue compatibility test and the distance between the donor's hospital and the transplant site is an issue that should be considered when conducting a future analysis. It is anticipated that these two parameters would have an impact on the total lung transplant costs for the NHS.

Exploratory model-based economic evaluation

Aim

The aim of this element of the analysis was to conduct an exploratory model-based economic evaluation of a UK adult lung transplant service that includes both EVLP and standard lung transplant compared with a service that only includes standard lung transplant. As was noted before, the data for this model came from the descriptive analysis described above and the available literature on lung transplantation.

Objectives

The objectives of this work were to:

- construct a decision-analytic model
- populate the model, as much as possible, with the DEVELOP-UK study data
- estimate the incremental costs per additional life-year gained (cost-effectiveness analysis) and per QALY gained (cost–utility analysis) comparing a lung transplant service including both EVLP and standard lung transplants with a service including only standard lung transplants.

Model structure

A decision-analytic model (*Figure 24*) was built in Microsoft Excel following the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines on conceptualising models.[55] The model represents the UK adult lung transplant service care pathway; beginning on the waiting list (state A) and progressing to being removed from the waiting list (state G); dying (state F); or receiving a standard (state B), or EVLP lung transplant (state D). From the lung transplant state, recipients progress either to death or, if they survive 1 year post lung transplant, to a post-lung transplant state; either states C or E depending on the type of lung transplant received.

The post-lung transplant states were split into first year post lung transplant (including the cost of the lung transplant), and from year 2 onwards. This method was chosen as existing evidence suggested that the first year post lung transplant is key and should be modelled separately.[56,57]

An area-under-the-curve Markov-type model was developed for post-lung transplant progression, where the length of time a lung transplant recipient survived from year 2 post lung transplant onwards was determined from a survival curve and allocated (as a fixed number of years) to each recipient in states C and E. To calculate the area under the curve, UK Cardiothoracic Transplant Audit survival data for 1, 3, 5 and 10 years post lung transplant were used and information on maximum life expectancy was

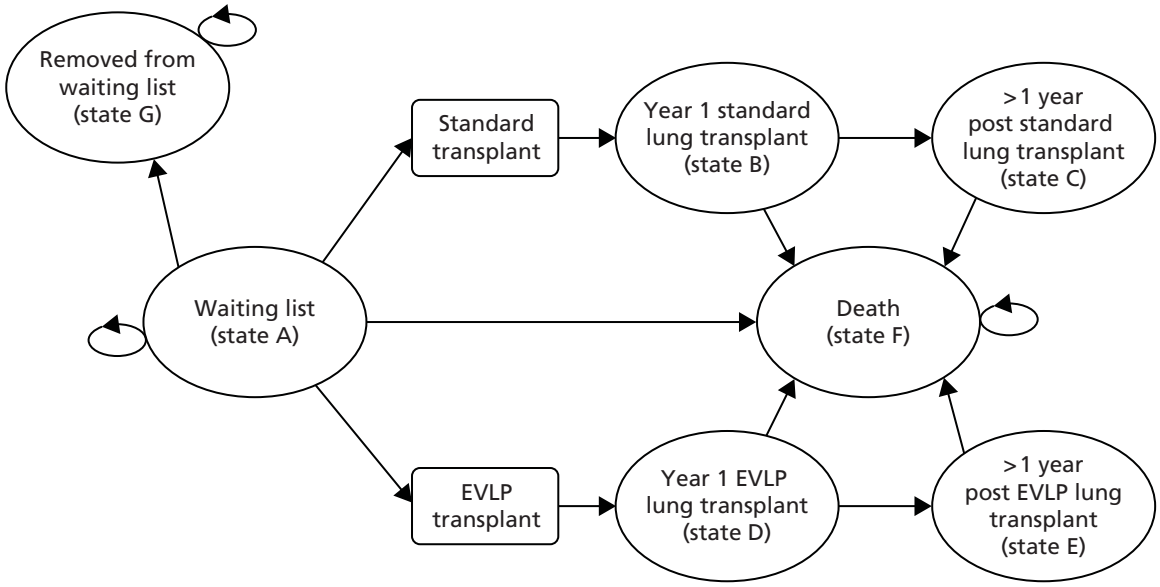

FIGURE 24 Model structure.

sought.[58] More precisely, the ISHLT data for adults receiving a lung transplant between January 1990 and June 2012 report that survival of 19 years post lung transplant is 12%.

Half-cycle corrections were used for life-years gained in line with ISPOR guidelines,[59] which are useful when the timing of the transition within the cycle is not known. On the other hand, no adjustment was made for QALY and cost calculations and, therefore, the QALY incremental cost-effectiveness ratio (ICER) would not be affected by the adjustment. A cohort of 1000 patients start in the waiting list state in the same year, and their progression was modelled over a lifetime horizon. The cycle length was 1 year, reflecting waiting list transitions and survival data.

Target population/location

The target population was adults on the UK lung transplant waiting list.

Study perspective

The perspective was the UK NHS using direct health-care costs only.

Comparators

The comparators are a UK adult lung transplant service that includes the use of both EVLP and standard lung transplants as the intervention (EVLP service) and a UK adult lung transplant service that includes only standard lung transplant as the control (standard service).

Time horizon

The time horizon used was lifetime, enabling consideration of costs and effects over the cohort's lifetime.

Discount rate

The base-case analysis used a 3.5% discount rate for both costs and effects following NICE guidelines.[52,60]

Outcomes

The principal outcome measure used was the QALY. Life-years gained was also measured, for the cost-effectiveness analysis, along with the number of lung transplants carried out.

Measurement of effectiveness/transitions

Lung transplant activity witnessed at the Newcastle centre during the study was used to inform the transition from waiting list to lung transplant in order to replicate within trial transitions. The Newcastle

centre was chosen as it was the largest study centre. During the trial, standard lung transplants increased by 25% at the Newcastle centre, and this increase was applied to the pre-study transition from waiting list to lung transplant to calculate a within-study transition. A 10% increase in lung transplant activity because of EVLP lung transplant, also witnessed during the study overall by all centres, was used to calculate the transition to EVLP lung transplant. The pre-trial transition was taken from NHSBT data.[61] For transitions from waiting list to removal from waiting list and to death, NHSBT transitions were used from a cohort added to the waiting list in 2010/11 and followed for 3 years (to 2013/14), 2 of which were during the DEVELOP-UK study, reflecting in-trial waiting list transitions.[62]

Post-transplant survival during the DEVELOP-UK study was not used to inform the model because of the small number of EVLP transplants carried out during the trial. In the absence of conclusive data from the literature, survival following EVLP and standard lung transplant were taken to be the same. Survival data were taken from the UK Cardiothoracic Transplant Audit, 1-year survival includes surgical mortality.[58] Area-under-the-curve methods were used to calculate a survival estimate that was applied to all recipients of a lung transplant who survived 1 year post transplant. The transitions used in the model are presented in *Table 43*.

Health state utilities

During the DEVELOP-UK study, SF-36 questionnaires were administered to participants while on the waiting list, and again at 3 and 12 months post surgery. The conversion of SF-36 data to utilities is described in *Analysis of quality of life*. For this exploratory analysis, average utility means were calculated for baseline/waiting list, 3 and 12 months post transplant. Post-transplant, separate utilities were allocated to the standard and EVLP transplant groups, and only survivor's utilities were included. Separate utilities for standard and EVLP were not allocated in the waiting list state, as some of the cohort patients will die or be removed from the waiting list, and it is important to capture these utilities as well as the transplant recipient utilities. The utilities used in the model are presented in *Table 44*.

Resources and costs

Costs were derived as described earlier in this chapter (see *Within-study descriptive analysis of costs and quality-adjusted life-years*) and used to populate the model with the exception of waiting list costs that were not available using the DEVELOP-UK study data. In this case, waiting list costs from Anyanwu *et al.*[65] were used to populate the model. These costs were the results of a published economic evaluation of adult lung transplantation in the UK. The costs for double lung transplantation waiting list were assigned to the model and inflated to 2013/2014 prices using the Hospital and Community Health Services's 2007/2008 and *Index 2013/14*.[51]

Costs in the transplant states B and D (year 1 standard/EVLP lung transplant) include the costs of donor hospital tests, lung retrieval, recipient preparation, EVLP procedure (if appropriate), lung transplant, inpatient post-operative care, and medication and outpatient costs for 1 year following transplant. Costs in states C and E (> 1 year post standard/EVLP lung transplant) are year 1 annual costs from the DEVELOP-UK study data, extrapolated forward using the data annual costs reported in Anyanwu *et al.*[65] The costs used in the model are presented in *Table 44*.

Assumptions

- It was assumed that patients removed from the waiting list no longer accrue costs or utilities, and so do not contribute further to model outcomes following removal.
- In line with survival rates reported by the ISHLT, it was assumed that no lung transplant recipients survive beyond 25 years.
- Waiting list transitions were available for only 3 years post registration and, as only 6% of the cohort was still on the waiting list after 3 years, it was assumed that all transitions remain linear from year 3 onwards, and would have little effect on the overall results of the model after year 3. For example, mortality for year 1 is 17% of the cohort, in year 2 it was 18%, and by year 3 it had only increased to 19% of the original cohort. The year 3 onwards transition to death is 0.02, and the remaining cohort is also small.

TABLE 43 Model transitions and survival: base case and scenario analyses

Parameters	Base case	Source	NHSBT 2013/14 transitions	Source	Pre-trial transitions	Source
Waiting list transitions						
Removal from waiting list						
Year 1	0.04	NHSBT 2013/14[62]	0.04	NHSBT's *Annual Report on Cardiothoracic Transplantation 2013–14*[62]	0.08	NHSBT's *Organ Donation and Transplantation Activity Report 2011–2012*[61]
Year 2	0.04	NHSBT 2013/14[62]	0.04	NHSBT's *Annual Report on Cardiothoracic Transplantation 2013–14*[62]	0.03	NHSBT's *Organ Donation and Transplantation Activity Report 2011–2012*[61]
Year 3 onwards	0.25	NHSBT 2013/14[62]	0.25	NHSBT's *Annual Report on Cardiothoracic Transplantation 2013–14*[62]	0.11	NHSBT's *Organ Donation and Transplantation Activity Report 2011–2012*[61]
Transition to death						
Year 1	0.17	NHSBT 2013/14[62]	0.17	NHSBT's *Annual Report on Cardiothoracic Transplantation 2013–14*[62]	0.17	NHSBT's *Organ Donation and Transplantation Activity Report 2011–2012*[61]
Year 2	0.08	NHSBT 2013/14[62]	0.08	NHSBT's *Annual Report on Cardiothoracic Transplantation 2013–14*[62]	0.09	NHSBT's *Organ Donation and Transplantation Activity Report 2011–2012*[61]
Year 3 onwards	0.02	NHSBT 2013/14[62]	0.02	NHSBT's *Annual Report on Cardiothoracic Transplantation 2013–14*[62]	0.17	NHSBT's *Organ Donation and Transplantation Activity Report 2011–2012*[61]
Transition to standard lung transplant						
Year 1	0.5	Freeman Hospital	0.5	NHSBT's *Annual Report on Cardiothoracic Transplantation 2013–14*[62]	0.4	NHSBT's *Organ Donation and Transplantation Activity Report 2011–2012*[61]
Year 2	0.56	Freeman Hospital	0.4	NHSBT's *Annual Report on Cardiothoracic Transplantation 2013–14*[62]	0.38	NHSBT's *Organ Donation and Transplantation Activity Report 2011–2012*[61]
Year 3 onwards	0.58	Freeman Hospital	0.069	NHSBT's *Annual Report on Cardiothoracic Transplantation 2013–14*[62]	0.28	NHSBT's *Organ Donation and Transplantation Activity Report 2011–2012*[61]

Parameters	Base case	Source	NHSBT 2013/14 transitions	Source	Pre-trial transitions	Source
Transition to EVLP lung transplant						
Year 1	0.050	Freeman Hospital	0.1			
Year 2	0.056	Freeman Hospital	0.08			
Year 3 onwards	0.058	Freeman Hospital	0.0138			
Increase in transplants	0.1	Freeman Hospital	0.2	Boffini *et al.*,[63] Cypel *et al.*,[30] and Henriksen *et al.*[64]		
Post lung transplant survival						
1 year survival (standard and EVLP)	0.766	UK cardiothoracic audit[62]				
Area under the curve						
1 year survival	0.766	UK cardiothoracic audit[62]				

TABLE 44 Model utilities and costs: base case and scenario analysis

Parameters	Base case	Source	Joint utilities	Source
Utilities				
Waiting list	0.563	DEVELOP-UK study data	0.563	DEVELOP-UK study data
Standard lung transplant			0.702	DEVELOP-UK study data
1 year post lung transplant	0.690	DEVELOP-UK study data	0.734	DEVELOP-UK study data
Year 2 onwards post lung transplant	0.728	DEVELOP-UK study data		
EVLP lung transplant				
1 year post lung transplant	0.793	DEVELOP-UK study data		
Year 2 onwards post lung transplant	0.782	DEVELOP-UK study data		
Costs				
Waiting list cost per year	£23,104	Anyanwu *et al.*[65]		
Transplantation costs: standard	£50,203	DEVELOP-UK study data		
Transplantation costs: EVLP	£133,342	DEVELOP-UK study data		
Post transplantation				
Standard lung transplant				
Year 1	£9405	DEVELOP-UK study data		
Year 2	£3696	DEVELOP-UK study data		
Year 3 onwards	£3400	DEVELOP-UK study data		
Area-under-the-curve cost: year 2 onwards	£24,693	DEVELOP-UK study data		
EVLP lung transplant				
Year 1	£5739	DEVELOP-UK study data		
Year 2	£2255	DEVELOP-UK study data		
Year 3 onwards	£2075	DEVELOP-UK study data		
Area-under-the-curve cost: year 2 onwards	£15,068	DEVELOP-UK study data		
Discount rate	0.035	NICE[60]		

- As no evidence of a difference in survival outcomes was found from a search of clinical trials comparing standard and EVLP lung transplants, it was assumed that survival post lung transplant is the same for standard lung transplant and EVLP lung transplant recipients.

Uncertainty in model parameters

The assumptions used in identifying and calculating parameters can introduce uncertainty into the model; this uncertainty can be explored using sensitivity analysis. In this analysis, two types of sensitivity analysis were used: scenario analysis and probabilistic sensitivity analysis.

Scenario analysis

Scenario analysis explores uncertainty in parameters by analysing results using plausible alternative parameters. Four scenario analyses were carried out, variations in parameter values from the base case are presented in *Tables 43* and *44*.

NHS Blood and Transplant 2013/14 transitions

In order to explore the choice of transition from waiting list to transplant, the transitions from the waiting list witnessed by all trial centres during the DEVELOP-UK study were used in a scenario analysis. The waiting list transition to lung transplant used in the scenario analysis was the waiting list transition published by NHSBT, plus an EVLP activity increase. To adjust for EVLP lung transplants carried out during the DEVELOP-UK study and included in the NHSBT figures, the transition to lung transplant was decreased by 5%. Leaving an estimated transition to standard lung transplant, an EVLP increase of 20% was used, reflecting levels reported in the literature.[30,63,64]

Joint utilities

The utilities used post transplant are separate for EVLP and standard lung transplant. However, the number of SF-36 questionnaires completed by EVLP recipients was low (seven at 3 months compared with 52 standard recipients, and six at 12 months compared with 48 standard recipients). An analysis was run using a joint mean utility for both EVLP and standard lung transplant recipients at 3 and 12 months post transplant calculated from the DEVELOP-UK study data.

NHS Blood and Transplant 2013/14 transitions and joint utilities

A separate scenario analysis was run, combining both of the above scenarios to reflect transitions witnessed by all trial centres, and using the more robust joint utilities.

Increase in standard lung transplant activity

This scenario analysis compared pre-trial NHSBT standard lung transplant transitions[61] to the within-trial Newcastle transitions without any EVLP procedures. In other words, it purely compared a standard lung transplant service using pre-trial transitions with a standard lung transplant service using the transitions witnessed at Newcastle during the trial.

Probabilistic sensitivity analysis

Point estimates were used in the model, which do not represent the statistical variability surrounding estimates of costs, effects and cost-effectiveness. For this reason, a probabilistic sensitivity analysis was conducted. Probabilistic sensitivity analysis assigns suitable distributions to each parameter and simulations are carried out, each of which select a possible value across all parameters at once. In this analysis, 1000 simulations were carried out, and results are presented as a cost-effectiveness plane, an incremental cost-effectiveness plane and a cost-effectiveness acceptability curve. Parameters used in the probabilistic sensitivity analysis are presented in *Table 45* and distributions used are described below.

- Waiting list transitions: a beta distribution was chosen to fit to binomial data from the NHSBT service for waiting list removal and death. For transition to lung transplant, a beta distribution was chosen using figures reported by the DEVELOP-UK study.
- Survival rates post lung transplant: a beta distribution was fitted using the 'methods of moments' technique described by Briggs *et al.*[66]
- Costs: a gamma distribution was fitted to costs using the methods of moments technique. Briggs *et al.*[66] report that a gamma distribution is constrained by zero and positive infinity, as are costs, making a gamma distribution a good representation for uncertainty of costs.
- Utilities: a beta distribution was chosen for utility values using the methods of moments technique as described above. Using a beta distribution is a practical approach when utilities are not near zero.

Model results

Cost-effectiveness results

The base-case cost-effectiveness results are presented in *Table 46*. The mean undiscounted lifetime cost of a lung transplant in the standard service was £66,208, whereas the discounted lifetime cost was £64,861. The mean undiscounted lifetime cost of a lung transplant in the EVLP service was £70,562, whereas the

TABLE 45 Parameters used in the probabilistic sensitivity analysis

Parameters	Alpha, beta	Distribution	Source/reference
Waiting list transitions			
Removal from waiting list			
Year 1	38, 184	Beta	NHSBT's *Organ Donation and Transplantation Activity Report 2011–2012*[61]
Year 2	3, 50	Beta	NHSBT's *Organ Donation and Transplantation Activity Report 2011–2012*[61]
Year 3 onwards	1, 19	Beta	NHSBT's *Organ Donation and Transplantation Activity Report 2011–2012*[61]
Transition to death			
Year 1	9, 213	Beta	NHSBT's *Organ Donation and Transplantation Activity Report 2011–2012*[61]
Year 2	2, 51	Beta	NHSBT's *Organ Donation and Transplantation Activity Report 2011–2012*[61]
Year 3 onwards	5, 15	Beta	NHSBT's *Organ Donation and Transplantation Activity Report 2011–2012*[61]
Transition to standard lung transplant			
Year 1	111, 111	Beta	DEVELOP-UK study data
Year 2	30, 23	Beta	DEVELOP-UK study data
Year 3 onwards	12, 8	Beta	DEVELOP-UK study data
Increase in lung transplant activity because of EVLP	4.3, 39	Beta	DEVELOP-UK study data
Post-lung transplant survival			
1-year survival standard and EVLP	1694.3, 517.6	Beta	NHSBT's *Annual Report on Cardiothoracic Transplantation 2013–14*[62]
Area under the curve			
1-year survival	1694.3, 517.6	Beta	NHSBT's *Annual Report on Cardiothoracic Transplantation 2013–14*[62]
3-year survival	1278.1, 770,2	Beta	NHSBT's *Annual Report on Cardiothoracic Transplantation 2013–14*[62]
5-year survival	947.0, 863.7	Beta	NHSBT's *Annual Report on Cardiothoracic Transplantation 2013–14*[62]
10-year survival	388.1, 777.3	Beta	NHSBT's *Annual Report on Cardiothoracic Transplantation 2013–14*[62]
Utilities			
Waiting list	2292.2, 1782.4	Beta	DEVELOP-UK study data
1 year post standard lung transplant	418.2, 187.6	Beta	DEVELOP-UK study data
2 years onwards post standard lung transplant	436.9, 163.2	Beta	DEVELOP-UK study data
1 year post EVLP lung transplant	69.6, 18.2	Beta	DEVELOP-UK study data
2 years onwards post EVLP lung transplant	22.4, 6.3	Beta	DEVELOP-UK study data
Costs			
Waiting list cost per year	100.0, 232.0	Gamma	DEVELOP-UK study data
Standard lung transplant	294.89, 170.24	Gamma	DEVELOP-UK study data
EVLP lung transplant	95.43, 1397.21	Gamma	DEVELOP-UK study data

TABLE 45 Parameters used in the probabilistic sensitivity analysis (*continued*)

Parameters	Alpha, beta	Distribution	Source/reference
Post-lung transplant costs – standard			
Year 1	90.61, 103.8	Gamma	DEVELOP-UK study data
Year 2	90.61, 40.79	Gamma	DEVELOP-UK study data
Year 3 onwards	90.61, 37.53	Gamma	DEVELOP-UK study data
Post-lung transplant costs – EVLP			
Year 1	19.55, 293.48	Gamma	DEVELOP-UK study data
Year 2	19.55, 115.34	Gamma	DEVELOP-UK study data
Year 3 onwards	19.55, 106.11	Gamma	DEVELOP-UK study data

TABLE 46 Base-case cost-effectiveness results

	Without EVLP	With EVLP
Costs (%)		
Waiting list	£9223 (14)	£7157 (10)
Year 1 post lung transplant	£43,259 (65)	£49,861 (71)
Year 2 onwards post lung transplant	£13,727 (21)	£13,544 (19)
Total		
Undiscounted	£66,208	£70,562
Discounted	£64,861	£69,358
Outcomes		
Life-years gained		
Undiscounted	5.61	5.63
Discounted	5.38	5.41
QALYs		
Undiscounted	3.63	3.68
Discounted	3.48	3.54
Incremental		
Costs		£4496
Life-years gained		0.03
QALY		0.06
ICER		
Life-years gained		£147,000
QALY		£73,000
Number of lung transplants		
Standard lung transplant	726	675
EVLP lung transplant		67

discounted cost was £69,358. In both services, the largest proportion of cost was the year in which the transplant took place, accounting for 65% of total lifetime cost in the standard service and 71% of total lifetime costs in the EVLP service. The incremental cost of the EVLP service was £4496, while the number of incremental life-years gained and number of QALYs gained was 0.03 and 0.06, respectively. The life-year ICER was £147,000, and the QALY ICER was £73,000.

In the standard service, the number of standard lung transplants carried out from a cohort of 1000 was 726. In the EVLP service, the number of standard lung transplants was 675 and the number of EVLP lung transplants 67, a total of 742; 16 (2%) more than the standard service.

Scenario analysis results

The scenario results are presented in *Table 47*.

2013/2014 NHS Blood and Transplant transitions

This scenario resulted in an incremental cost per QALY gained of £40,000. The number of lung transplants carried out was 644 in the standard service, and 709 in the EVLP service; thus, there was an increase of 65 lung transplants (10%).

Joint utilities

This scenario resulted in a QALY ICER of £124,000. The number of lung transplants carried out was 726 in the standard service and 742 in the EVLP service, as in the base-case analysis.

Combining NHS Blood and Transplant 2013/14 transitions and joint utilities

This joint scenario resulted in a QALY ICER of £51,000. The number of lung transplants carried out was 644 in the standard service and 709 in the EVLP service, as in the NHSBT 2013/14 transitions scenario.

Standard lung transplant only

This scenario resulted in a QALY ICER of £7000. The number of lung transplants carried out was 620 in the pre-trial standard service and 726 in the 'Newcastle experience' service, an increase of 106 lung transplants (17%).

Probabilistic sensitivity analysis results

The results of this analysis are presented for the cost–utility analysis only. The ICER was £72,000, similar to the base case. *Figure 25* shows the predicted cost and QALY plots for each intervention, whereas *Figure 26* shows the predicted plots for the difference in costs and QALYs between the two interventions, with a threshold of £30,000 per QALY. *Figure 25* indicates that the EVLP service is marginally more effective and costly than the standard lung transplant service. *Figure 26* indicates that the majority of the simulations fall in the north-east quadrant, where the EVLP service is more costly and more effective than the standard service, but several simulations fall into the north-west quadrant of the figure, where the EVLP service is less effective and more costly than standard service. The incremental effectiveness in QALYs varies between –0.05 and 0.3, with a mean of 0.061 (95% CI –0.006 to 0.152), and the incremental costs vary between £680 and £16,180 with a mean of £4349 (95% CI £1167 to £9742).

The data from the Monte Carlo simulation were used to plot a cost-effectiveness acceptability curve (*Figure 27*). The results indicate that at the typical ceiling ratio adopted by NICE of £20,000, the standard service has a 99.9% chance of being considered cost-effective compared with the EVLP service.

The conclusions of the economic evaluation are discussed in *Chapter 6*.

TABLE 47 Scenario analysis results

	Without EVLP				With EVLP					ICER	
	Transplant cost	Adjusted total life-years	QALYs	Number of standard lung transplants	Transplant cost	Adjusted total life-years	QALYs	Number of standard lung transplants	Number of EVLP lung transplants	Life-years	QALYs
NHSBT transplant transitions	£64,902	5.15	3.27	644	£72,638	5.30	3.47	591	118	£52,000	£40,000
Joint post-transplant utilities	£64,861	5.38	3.51	726	£69,358	5.41	3.55	675	67	£147,000	£124,000
Combining both scenarios	£64,902	5.15	3.30	644		5.30	3.45	591	118	£52,000	£51,000
Standard lung transplant only	£62,240	4.95	3.13	620		5.38	3.48	726	0	£6000	£7000

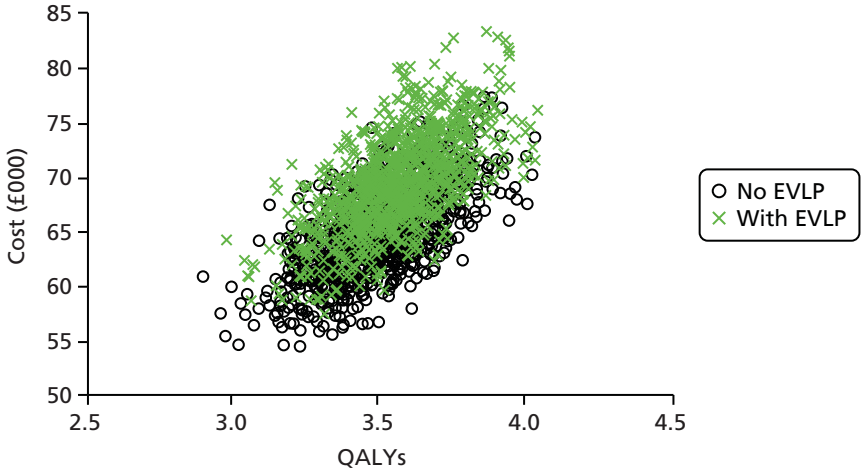

FIGURE 25 Cost-effectiveness plane.

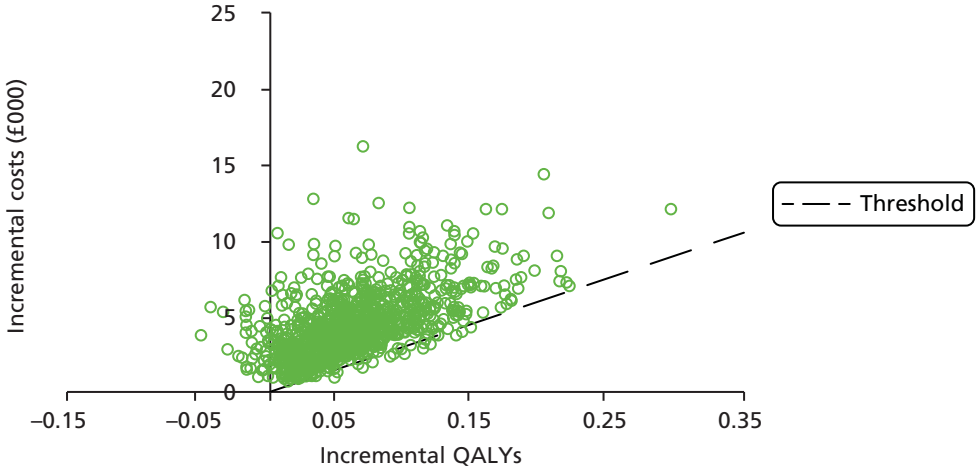

FIGURE 26 Incremental cost-effectiveness plane.

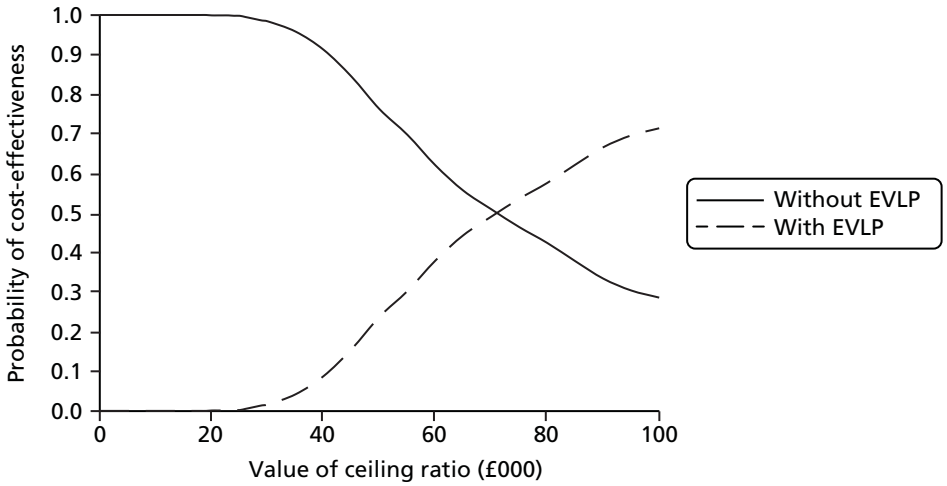

FIGURE 27 Post-trial cost-effectiveness acceptability curve.

Chapter 5 Qualitative study results

Introduction

There is currently no published literature examining patients' views of EVLP, and research related to people's experiences of receiving donor organs is also limited.[67–72] It is imperative that if new heath-care technologies, such as EVLP, are to be implemented successfully and achieve real benefits for patients, the views of those receiving them are taken into account. This substudy critically examined patients' attitudes towards, and understanding of, EVLP; their reasons for participation in the DEVELOP-UK study; and their experiences of waiting for and receiving a transplant.

Research objectives

The aim of this 24-month qualitative substudy was to identify, describe and understand patients' pre- and post-operative perceptions of EVLP, and to explore how these are mediated by individual, social, physical and clinical factors.

Methods

This qualitative study used focused interviews to explore patients' views and experiences of consenting to be part of DEVELOP-UK study and their views of EVLP both before and after transplantation. Focused interviews are particularly useful when researching a new area about which relatively little is known.[73] This substudy was conducted with patients from two study sites: the Freeman Hospital, Newcastle, and Harefield Hospital, London. These two sites were chosen as they both provide care to diverse populations across large geographical areas, and they were expected to recruit the largest number of patients to the DEVELOP-UK study.

Prior to commencing data collection, an outline interview topic guide was developed that covered the following key areas:

- pre transplantation
    - patients' understandings of EVLP and the perceived acceptability of this procedure in comparison with other donor lungs
    - patients' hopes and expectations for EVLP
    - patients' accounts of their own health and experience of living with their condition
    - patients' experiences of waiting for lung transplantation
- post transplantation
    - patients' retrospective accounts of their pre-operative health and experiences
    - patients' accounts of waiting for a transplant
    - patients' views and experiences of receiving and living with an EVLP or standard transplant.

Sampling

The aim of this substudy was to sample a smaller group of patients from the DEVELOP-UK study to explore their views and experiences in more detail. Initially the plan was to recruit between 20 and 30 adult patients waiting for lung transplantation and between 20 and 30 patients 3–6 months post-operatively

from across both sites. Maximum variation purposive sampling[74] was used to ensure that a range of different experiences was included; specifically, we sampled for: sex, age, location (distance from hospital), diagnosis and length of time on the transplant list.

On consenting to take part in the DEVELOP-UK study, pre transplantation patients were given some brief information about the qualitative substudy and, if they were willing to consider taking part, they were asked to sign an EOI form. On completing an EOI form, patients were then given further detailed information about the qualitative substudy by a research nurse. After this, if patients were still willing to take part, they completed a consent to contact form, which was passed to the qualitative research team. The patients were subsequently contacted by a qualitative researcher and were again given another opportunity to ask further questions. If they were still interested in taking part, a date for interview was organised and a consent form was mailed out for the patient to complete and return. It was made clear to patients at all times that participation in any interviews was optional. During recruitment the team used purposive sampling, as outlined above, and reviewed the sample regularly to ensure that a range of different views and experiences was included, and actively targeted under-represented groups (e.g. patients with CF, younger patients, etc.). At the end of their first interview, patients were asked if they were willing to be interviewed again and all agreed, although only seven of the 26 patients interviewed pre transplantation were able to be interviewed again, as the remainder either had not received a transplant within the timescale for the fieldwork or were not well enough to be interviewed again.

Owing to the nature of the sampling for the study, not everyone who returned a consent to contact form was actually invited to interview before their transplantation. However, following transplantation, a number of patients who had previously returned consent to contact forms to the team but had not already been interviewed were contacted again 3 months post transplantation by a researcher and invited to take part in an interview at this stage. Upon receipt of consent to contact forms, an additional 11 individuals were invited to take part in an interview 3–6 months post-operatively.

As only a small number of EVLP transplantations were undertaken there were only a few people who could be interviewed about this experience. A targeted effort was made to identify and recruit all EVLP patients to the qualitative substudy. However, some patients, although they had expressed an initial interest in being interviewed, did not return a consent to contact form.

Interviews

Individual interviews were conducted either face to face or by telephone by JL. The first three pre-transplantation interviews were carried out in participants' homes. Subsequent interviews were conducted either face to face in a room at the hospital when the patient attended for outpatient review or by telephone at a time that was convenient to the participant. All except two post-transplantation interviews were conducted by telephone. Telephone interviews were particularly useful in this study as they allowed the team to interview people who lived across a wide geographic area. Transcripts of early face-to-face interviews were carefully compared with initial telephone interviews and there appeared to be little difference in the quality or detail of the data collected.

Data analysis

Following a long tradition in qualitative research,[75,76] data collection and analysis occurred concurrently to allow for issues or themes that were identified in earlier interviews to be explored in more depth in subsequent interviews. All interviews were digitally audio-recorded and transcribed verbatim. Initially, interview transcripts were checked against the audio-recording and, in line with Data Protection Legislation and Research Governance stipulations,[77] all potentially identifiable information pertaining to individuals was anonymised. After this, transcripts were read; open, then focused, coding was undertaken; and emergent codes from the analysis of this stage were presented to the wider research team for checking and validity. The validity of data interpretation was ensured by independent coding and cross-checking by the qualitative research team (JL and CE). Data collection stopped when no new themes were being identified in the data. NVivo version 10 (QSR International, Warrington, UK) was used to facilitate data analysis management.[78]

Results

In total, interviews were conducted with 44 participants (24 men and 20 women) aged 21–69 years. Of these, only 19 were interviewed before transplantation, seven both before and after transplantation and 11 after transplantation.

Patients were located across a wide geographic area across the UK, Ireland and the Channel Islands. The patients interviewed had been diagnosed with a range of conditions: pulmonary fibrosis ($n = 7$), emphysema ($n = 9$), CF ($n = 8$), α_1-antitrypsin deficiency ($n = 5$), idiopathic fibrosis ($n = 2$) and others ($n = 6$). Twenty-six interviews (14 Newcastle; 12 Harefield) were conducted before transplantation with 12 women (aged 23–61 years) and 14 were with men (aged 25–69 years). Eighteen interviews were conducted post transplantation (13 Newcastle; 5 Harefield) with eight women (aged 21–62 years) and 10 men (aged 25–69 years). Two patients interviewed had received an EVLP transplantation, the rest a standard transplantation. Seven people (two women and five men) were interviewed both before and after transplantation, and, as outlined above, a further 11 (six women and five men) were interviewed only after transplantation.

Patients' views and understandings of ex vivo lung perfusion

One of the main foci of the qualitative substudy was to explore patients' views and understandings of EVLP and their expectations and hopes regarding the use of this new transplantation technology. Patients were asked to explain their understandings of EVLP. When asked specifically to explain EVLP, most people identified the perfusion process and the effect it had on the lungs as the major difference between an EVLP transplant and a standard transplant. Reference to a 'cleaning out', 'improving' the quality of the lungs was frequently mentioned, and some patients demonstrated a good understanding of the processes involved in EVLP:

> *I understand to be the sort of passing of some magic liquid through the lungs while they are ex vivo, i.e. after they have been removed from the donor to (a) deal with any bugs and whatever but also as I understand it to potentially improve their quality or bring them up to what they, you know for reasons of bugs.*
>
> *Dominic, pre transplant, centre 1*

> *They are pumped through with various different gases and a fluid to clean out and sort of recondition these lungs into a better condition so that they are suitable for transplantation.*
>
> *Mark, pre transplant, centre 2*

When describing EVLP, participants tended not to use technical language or give detailed information about the perfusion process. Rather, their explanations focused on what they appeared to regard as the essential information, that EVLP can enhance the quality of lungs, which previously would not have been suitable for transplantation so they could now be used:

> *They take somebody's lungs that may have been a smoker and they basically recondition them. Clean them on the machine and then pass them onto the patient that's needing them.*
>
> *Adrian, pre transplant, centre 2*

> *It's retrieving a pair of donor's lungs that you're not sure if they're 100%, so they're put on like a heart lung by-pass machine and cleansed out given fluids and taken all the muck out, and replenishing as soon as they then can be used as a donors [and] transferred to somebody waiting for them.*
>
> *Amanda, pre transplant, centre 1*

Patients were asked how they would explain the process of EVLP to family and friends, and some used analogies to help explain EVLP to their families in everyday terms:

> *Well, I think I explained it as being like a washing machine where they take, put the lungs in, give them a clean, give them, fix them up and then just let them dry out a little bit.*
>
> *Angela, pre transplant, centre 2*

A service that's basically what is was, you're putting them in basically, donor lungs going for a service or an MOT [Ministry of Transport test] you know just like your car.

Tom, post transplant, centre 2

Although most patients were able to articulate a clear and accurate explanation of EVLP, a small number of people at both sites gave less accurate or confused explanations of EVLP:

My understanding of it is that it's organs taken from long-term ill patients that perhaps have been on a life-support machine for several months and died very slowly and as the organs, you know as the body dies so the organs you know they lose their selves and they just get weaker and sort of die along with the patient and you know they've found that they're able to revive these lungs and bring them back into working order.

Christine, pre transplant, centre 1

Pickled lungs, pickled lungs. I keep saying to everybody that they pickle the lungs. A set of lungs out of a donor; something wrong with them; they put them in whatever, hoover them out, give them antibiotics, clean them and everything, and hopefully get them up to a standard where they can be transplanted.

Sarah, pre transplant, centre 2

When patients consented to take part in the DEVELOP-UK study they were given a lot of information about the study, and were given several opportunities to ask questions and to clarify anything that was unclear to them. However, some patients still felt the need to seek out additional information about EVLP, often from the internet to supplement their knowledge. Patients in the DEVELOP-UK study also referred to having also consented to participate in other studies. They were willing to do this, however, consenting to several studies with large amounts of complex information sometimes led to some confusion about the details of individual studies:

Oh basically a pair of live lungs isn't it, they're not put on ice as it were. They're kept pumping using the donor's blood, yeah? I think I've got the gist of it.

Joseph, pre transplant, centre 1

Consenting to be part of the DEVELOP-UK study

During the interviews, participants were asked why they had made the decision to take part in the DEVELOP-UK study to explore the motivations of people consenting to be part of a trial of a new technology. Unsurprisingly, the most common reasons patients gave for consenting were the hope of receiving a transplant quicker and the possibility of helping others in the future:

Well my mum like said to me right 'You would have a better chance of getting a transplant if you go with that'. But I had already made my mind up that it is something that – you've got to really give it a go because you can double your chances really, can't you?

Jack, pre transplant, centre 2

I'm interested in the greater good not just my own good [OK] and I think you know I don't see how we'll ever make leaps forward in this stuff unless people are prepared to take a few chances.

Ali, pre transplant, centre 1

For a few, consenting to be part of a trial involving a new intervention was a difficult decision and required considerable time and thought:

No like at first I, I'm sort of thinking oh, oh my goodness, know what I mean? What about I mean what, who it was, he's [donor] got AIDS [acquired immunodeficiency syndrome], somebody's got this. Know what I mean, and somebody that like smokes you know a 100 fags a day sort of thing and that so I was initially, I thought at first until I read into, looked into it I thought I was getting the rough end

of the deal to be honest. You know whereas now, you know I've spoke to Karen [transplant co-ordinator] about it and she just says . . . we wouldn't go with them unless we're 100% sure, they've got to be as good as the other ones they would have used in the first place.

Connie, pre transplant, centre 2

Others expressed some reservations about the technology or limited understanding, but were willing to put their trust in the medical team who they believed would make the best decisions for them:

I wasn't really sure at first but then the more I was thinking about it, basically the doctors are always going to do their best for you so they are not going to give you something they think isn't going to work or anything like that so I wasn't really phased. To be honest I wasn't going to really think too much into it. Like even the [standard] transplant I didn't want to think too much into it I just wanted the doctors to do their job and just not really think about it.

Brenda, post transplant, centre 1

I put my faith in the people that are doing the operation. And, I mean, if they decide that lung's good enough for me, that's basically, good enough for me.

Adam, pre transplant, centre 2

However, patients' accounts demonstrate that, regardless of any fears, concerns or limited understanding of receiving EVLP lungs, they were aware that the lungs they received would function better than the ones they currently had.

What are my, well I'm hoping that the lungs will just be good enough, I get called up, get transplanted, and that even if its 80% better than what I've got now you know, I just know I've got faith in the system that you just wouldn't give me a crap pair of lungs really.

Amanda, pre transplant, centre 1

Going on the transplant list

Understanding of EVLP and motivation to take part in the DEVELOP-UK study were of interest to the research team. For patients themselves, being asked to take part in a study employing a new technique to increase the number of lungs available for transplantation appeared to be less significant than actually accepting the need to be placed on the transplant list in the first place. During the interviews, patients spoke in detail about what happened when they were accepted onto the transplant list, what they expected the transplant process to be like and what they were fearful of. Many of the views in this following section relate to transplant generally rather than EVLP specifically, but provide an insight into patients' broader experiences of waiting for a transplant.

During interviews, patients spoke about their condition needing to deteriorate to a point where the transplant team would consider them to be at a stage where a transplant would be the best option:

I was too fit to go on the transplant list then I think. So it well I wasn't overly disappointed, I was disappointed slightly but I wasn't overly disappointed if you know what I mean because I knew that I was still fit enough I was still breathing not too badly I am saying not too bad I was absolutely atrocious but you know what I mean compared to near the end.

Paul, post transplant, centre 2

On being accepted on to transplant waiting list all patients interviewed expressed feelings of hope, relief or joy:

[I] absolutely burst into tears when they told me that I was going on the transplant register, it was like you were getting some form of a lifeline.

Mark, post transplant, centre 2

However, they were aware that if their health deteriorated too much they might be removed from the transplant list:

> *Well what it is you see it's like a window, it's you've not got to be too ill but you've not got to be too well, you can't be either side of it you've got to be right.*
>
> *Connie, pre transplant, centre 2*

> *The only thing that I'm really scared of is because each time I get a chest infection now it comes worse each time and the last time I had one well I thought, either, you know, I think I should have been in hospital really but I couldn't even walk to the toilet but we just got another load of antibiotics so I've learnt by that mistake or experience and next time I'll get the doctor in or get my husband to take me to hospital but and so the only thing that worries me is that I'll die of a chest infection so that's the scary bit.*
>
> *Amanda, pre transplant, centre 1*

Several patients spoke about their fear regarding the transplant operation, but acknowledged this had to be balanced by the fact that transplantation was their only hope of survival:

> *I'd be lying if I said I wasn't frightened, because I think everybody who's facing any kind of surgery is worried, apprehensive about it. But it was a choice of sitting in a chair, or having a chance. And I chose the chance. I don't want to be sitting in this chair.*
>
> *Sarah, pre transplant, centre 1*

> *Well dying more than owt [anything]. It's just all going wrong and the first thing you hear like the first thing you hear is like the rates that's successful and then not successful and it were just like – I think it was an 80% chance of it being successful and 20% that it been not be successful. That is all you can think about really, is that 20% really if its. That's all I kept thinking about. But now I've like kind of thought if you don't have it done you are going to be that 20% anyway, if so I could as well just take risk.*
>
> *Jack, pre transplant, centre 2*

Being on the list

One of the main topics discussed in detail by patients during their interviews was their experience of living their life while waiting on the transplant list. Although not specifically related to EVLP, it demonstrates the ways in which people adapt to a life waiting for a transplant. However, some of the everyday difficulties encountered may offer some insight into why people were willing to consent to be part of a study involving a new technology that could increase their chances of receiving a transplant sooner. Although patients' experiences varied, the data suggest that waiting for a transplant had a significant impact on all of their lives. Some people continued to try to do many of their normal activities, whereas others worked hard to become fitter and more active to enhance their chances of a successful transplant:

> *As I got put on transplant list like I just knew I'd got to make sure I was fit enough and healthy enough to get through this operation if and when it happened. Well just tried to, well I went on exercise bike, you know do as much as I could on exercise bike, walking up and down us [our] drive and obviously not in bad weather but I just do a bit more walking around the house and just doing general housework you know what I mean trying to keep on top of everything.*
>
> *Adrian, pre transplant, centre 2*

Once accepted onto the transplant waiting list patients must adjust to a different way of living; many patients referred to feeling constantly on the alert waiting for a telephone call about a potential donor and needing to be ready to leave for the hospital when the call came:

> *I can't go here, I can't go there without thinking am I going to get a call. I always have my phone with me, my phone is always on loud, it's always in my hand. I'm constantly staring at it, every time it goes,*

makes a noise, my heart stops and it's just crazy and it's really annoying cos I can't go on holiday . . . I can't even leave the county . . . so I basically I am trapped, it's literally like being in a cage.

Angela, pre transplant, centre 2

As well as affecting their lives, participants also spoke of the impact of waiting on the lives of their families and significant others:

Yeah it's horrible, because you can't relax, no you, I know it sounds, phone rings and your hearts in your mouth you know, is it that, is it this? My husband I mean he, he doesn't want much but now and again he goes out. He can't go out, all over Christmas week we couldn't make arrangements to go anywhere or, you know you can't go out and have a drink . . . You know so it, it's like you're sort of waiting with bated breath sort of thing.

Connie, pre transplant, centre 2

On being accepted onto the waiting list after their assessment, all participants spoke of going home to pack their bags in preparation for being called in for a transplant. For many their initial feeling of anxiety and/or expectation of a rapid transplant was replaced by the reality of being on the waiting list and sometimes despondency:

I packed a suitcase. Bought new pyjamas and everything, and it's been packed for a year. Packed and unpacked and washed and put there. But it's there.

Sarah, pre transplant, centre 2

Some participants spoke of being called into the hospital several times for potential transplants that failed to progress. These 'false alarms', as the patients called them, raise expectations and can be very disruptive, particularly for those travelling long distances to the hospital. However, false alarms could also be reassuring, either because this appeared to convey that they were at the 'top' of the list, or because it helped to orientate them towards the process:

I got the stockings on this time. Got the shower, got the gown on . . . Got the white stockings on. Had the heart trace and the X-ray and all the bloods taken. So this was the farthest we've getting this this time. I have actually been in the gown the last time, but that's as far as it's gone. But this time was a little bit further, and I keep thinking, 'Getting a little bit. She's putting stockings on; I've never had them on before'. You know, 'Yes!' A step closer, but it wasn't to be. It just wasn't to be.

Sarah, pre transplant, centre 2

Sarah saw the fact that she had different things done each time as a sign that she was getting further along the line, nearer to her transplant: these may not have the significance that patients assigned to them.

Waiting for a suitable donor organ to become available could take many months or years, and, although patients were waiting, they were conscious that their condition was deteriorating and that they could die while waiting for a transplant. Connie spoke about treating each significant life event such as Christmas and birthdays as her last, although she did not share this with her family:

I don't know you see it's like having like, how do I explain it? . . . this Christmas well I've seen that as my last Christmas that's on your mind all of the time. Do you understand what I mean? And that's there every day. It's the only thing I haven't said [to my family] . . . you just feel that everything's your last Christmas, your last New Year, it's your last, every hurdle you can't see beyond it and I still can't. You can't dwell on it but it's there, it's like a dark shadow on you all the time, that's the best way, it's so hard to explain.

Connie, pre transplant, centre 2

Waiting for a transplant means waiting for someone else to die for their chance of survival, something that was not discussed in detail by many people. One exception was Annie who spoke about it being a circle, a link between the patient, the donor and the donor's family:

> *And it's not just a donor's lung; you know, somebody's got to die for you to have their lungs. And I mean, that must be horrendous for their family as well, so it's not just you; it's a proper little circle. It's just amazing.*
>
> *Annie, pre transplant, centre 2*

Perhaps to counter or cope with the anxiety and stresses of being on the transplant list, many of those interviewed made extensive plans for their lives post transplantation. These hopes ranged from the mundane to new challenges. Some patients saw their goal as undertaking new physical challenges, others just want to get back to 'normal', look after their grandchildren, go on holiday; the majority were happy to be able to do the mundane everyday activities they have missed:

> *I've got a walk planned with a friend and a dog on a beach! And then I just hope to get back to riding again.*
>
> *Christine, pre transplant, centre 1*

> *I look after my 4-year-old granddaughter quite a lot and sort of, although I'm fine with her because we do a lot of sitting down things, it would be nice to go back to sort of going out with her and things you know and just generally getting back to normal.*
>
> *Julia, pre transplant, centre 1*

Post-transplant experiences and hopes

Of the 18 patients interviewed post transplantation, seven had been interviewed before their transplantation as well, and 11 were interviewed only after receiving their transplant. Two people had received an EVLP transplantation. All the data from post-transplantation interviews are presented together for two reasons: first, to protect the anonymity of the small number of EVLP patients; and, second, from these two interviews it is not possible to ascertain any obvious differences in the reported experiences.

When participants described the events leading up to their transplant, they were often very specific about events, timings and how they felt. Some details they could recall themselves, and other aspects they had been told by relatives after the operation:

> *It was 1.30 in the morning, no sorry it was 9.30 on the Thursday night the phone rang again, it was Karen [transplant co-ordinator] and she said guess what I've been made an offer she said but someone else has also been offered the organs so start making your way to the hospital. I started getting prepped yet again and about quarter to five in the morning Karen got a call from the retrieval team to say, the organs are good it's a go ahead. So I was then wheeled down to theatre at about 5.30 that was the last time I saw my wife then. Surgery commenced around 5.30 in the morning, 5.30/6.00 in the morning and I believe it took about 10/10.5 hours.*
>
> *Mark, post transplant, centre 1*

A key factor in the transplant process is the need for a donor. Those patients who mentioned the donor referred to the emotion and grief that they felt for the donor's family and the effect it had on them, which varied between individuals:

> *Yeah it was definitely emotional time, there's no doubt about that, thinking about the donor, donor family all the time. Quite a lot of tears, emotional having to you know, them to pass away for me to live like you know. And it's not an easy thing to digest you know . . . I suppose the whole emotional*

thing was that I was alive and that someone had lost a brother, a dad, a husband you know a friend it was very raw for a long time and I just couldn't, I'd be walking down the corridor and just fall out crying you know any little small thing at all emotionally would set me off so actually recently we sent a letter to the donor's family which helped a lot like and hope to God helps them as well, like you know I wanted to show that I was up and about and achieving stuff before I sent the letter rather than send it at the saying thanks kind of gave them hope what I was beforehand and what my life is today yeah, so it was mentally tough and anything at all, even a song or something on the telly would set you off like you know you ended up watching cookery programmes.

Barry, post transplant, centre 2

Several participants spoke of wanting to make contact with the donor family to thank them and show how well they were doing, but were uncertain as to how this would be received:

What can you do that has any impact on anyone to say thank you? I mean you can write a letter and say thank you and if they get it, even better, but it's . . . might be a crumb comfort I suppose. If you say who you are in terms of middle-aged or you know, whatever – do they say 'Christ, what a waste, why didn't it go to a younger patient?' – All those conflicts, you know.

Tim, post transplant, centre 1

In addition to talking about their donors, participants spoke of their physical recovery post transplantation and their plans for the future. For all patients the first thing they recalled was the sensation of being able to breathe without struggling. For some this new way of breathing took a while to get used to:

I found the breathing quite hard because I didn't understand what was going on and I had to kind of make myself do it [right] I didn't trust it to do it on its own. It was a very strange experience [right] especially at night I was frightened to go to sleep in case it stopped because it felt so different. It's very eh and the fact that the even now the breath is such a long breath in I think I'm going to stop breathing because it's such a long time. Yeah I think it is you think oh god it can't really be that slow a breath surely but then you think well it's 3 litres instead of 0.5.

Beth, post transplant, centre 2

Some participants also experienced new health problems that they believed were in some way related to the transplant or post-transplant medication. However, the majority felt that living with their new health problem was not a significant issue compared with their condition pre transplant.

After receiving a transplant many patients expected to return to 'normal' life, restart work, go on holiday, start running. However, this was not always straightforward or at the rate hoped for, leaving some feeling disappointed:

It's been ok since I'll still be out, I'll still be out of breath, I'm not, I'm not 100% there's a lot of things I still can't do I can't like, I can walk into town but there, I got, I got to rest and I get out of breath very quickly there're certain jobs I do I get dizzy quickly but other than that, no, I'm fine it's good.

Keith, post transplant, centre 2

Chapter 6 Summary of study findings and discussion

Lung transplantation is the only therapeutic option for many patients with life-threatening chronic lung disease. The main factor limiting access to this life-saving therapy is the availability of suitable donor lungs. The consequences of this are a significant risk of death while on the waiting list for lung transplantation that, in the UK, for some disease categories, reaches > 30%. The development of EVLP to allow more objective assessment of organ suitability and potentially for reconditioning them has been heralded as a major breakthrough and represents the current frontier in advancing the impact of solid organ transplantation.

In the DEVELOP-UK study, all five UK adult lung transplant centres came together to investigate the possible impact that access to EVLP assessment and reconditioning of donor lungs might have on lung transplantation activity in the UK. Our hope was that EVLP would safely increase lung transplant activity by using more of the donor lungs that are already available, but that are currently felt to be unsuitable. The original hypothesis under investigation was that EVLP assessment and reconditioning of unsuitable donor lungs would produce survival in the first year after lung transplant that was non-inferior to that after standard lung transplantation.

The trial aimed to evaluate the clinical effectiveness of EVLP in increasing UK lung transplantation activity and, specifically, to demonstrate comparable outcomes for patients who received donor lungs exposed to EVLP compared with patients who received standard donor lungs. A within-study economic assessment aimed to evaluate the cost-effectiveness of generating more lung transplants by using EVLP, including modelling what sort of activity levels and costs would make it an intervention that could be adopted into standard use. Finally, the investigators were keen to know how patients waiting for lung transplantation felt about EVLP and use of donor lungs that might not otherwise have been deemed suitable.

The primary outcome measure of survival in the first year after transplant was chosen as a clinically meaningful unequivocal end point. The known historical frequency of mortality events in the first year after standard transplant from the Royal College of Surgeons UK audit[58] meant that there were solid data that could be used to calculate a sample size for the study to ensure that it was adequately powered.

Our main finding showed that survival in patients receiving a lung transplant after EVLP was not as good as in those who received a standard lung transplant. The Kaplan–Meier estimate of survival at 12 months was 0.67 (95% CI 0.40 to 0.83) for the EVLP arm and 0.80 (95% CI 0.74 to 0.85) for the standard arm, and the Cox hazard ratio of 1.96 (95% CI 0.83 to 4.67) equated to just less than twice the risk of death in first year in the EVLP arm.

The study was, however, terminated early because of slow recruitment and a concern about high levels of ECMO use, and the sample size of 18 in the EVLP arm is too small to allow firm conclusions to be drawn. There are a number of small studies published that include data on 1-year survival rates after lung transplantation with EVLP-assessed donor lungs, these ranged from 67% to 95%.[24,79] In the only larger study looking at longer-term outcomes including the risk of developing chronic lung allograft dysfunction, the group in Toronto showed 1-year survival of 79% in their EVLP group ($n = 63$) and 85% in their standard group ($n = 408$) with no statistical difference.[80] These data come from a single-centre experience performed outside a clinical trial and, therefore, are not directly comparable with the results of the DEVELOP-UK study.

When mortality events were compared by the EVLP protocol used, the hazard ratio for the hybrid protocol relative to the Lund protocol was 2.92 (95% CI 0.53 to 15.95). The outcomes for the 10 EVLP patients in the Lund protocol group were actually very similar to those in the standard transplant group with a

Kaplan–Meier estimate of survival at 12 months of 0.80 (95% CI 0.41 to 0.95). This raises the possibility that, had the study continued longer using the Lund protocol, robust conclusions could have been achieved. When examining the causes of death in the SAE reports, it became clear that they were not causally related to EVLP but as result of other complications that can occur after any lung transplantation. It is therefore possible that the higher risk of death seen with the hybrid protocol was as a consequence of small numbers in the study at that time rather than the protocol itself. There is a risk in overinterpreting the higher death rate in the EVLP arm as a whole because of the small numbers and the change in the EVLP protocol used.

The secondary outcomes used in the study were all key clinically relevant measures that indicate success of lung transplantation. Several of these, such as duration of ventilation or length of ITU stay, can be subject to variation that may not be due directly to the effectiveness of lung transplantation, as they can be influenced by factors outside the lungs. We showed that those in the EVLP arm of the study spent longer intubated (median 72 hours vs. 38 hours) and longer in the ITU, by a median of 10 days, than recipients of standard lung transplants. However, the time to discharge from hospital after the transplant was very similar.

These observations fit well with our cautious finding (given the limited sample size) that there was more severe early PGD in the EVLP group and a much higher rate of ECMO use for severe graft dysfunction, but that once the patients recovered from this early graft dysfunction, they made a good recovery to match the time to hospital discharge of the standard group. The largest difference in rates of severe PGD grade 3 was seen at baseline, which relates to that recorded on immediate return from theatre to the ITU, where 88.9% of the EVLP group had PGD grade 3. However, over the next 72 hours the rates of PGD grade 3 equalised between the EVLP and standard transplant group (27.8% vs. 22.5%, respectively). It is worthy of note that the rate of PGD grade 3 at 72 hours was higher than expected in the standard group at > 20%.

The PGD grade 3 rates in published studies in the first 72 hours after transplant range from 0% to 14%.[29,81] In a smaller recent study of eight EVLP transplants, the PGD grade 3 rate at baseline was 37%, but this dropped to 0% at 72 hours; two of these eight (25%) EVLP patients required ECMO support.[82]

There was a 10-fold increased use of ECMO in the EVLP arm, with 7 of the 18 patients requiring ECMO. Interestingly, there was no association between use of ECMO and early death as a result of graft failure, as six of the seven patients needing ECMO were successfully discharged from ITU. The duration of ECMO support was short, with the majority weaned off within 72 hours. The exact reason for very high levels of early severe PGD and ECMO use in the EVLP group is not clear, but one possibility is that the use of cardiopulmonary bypass during the transplant surgery might have caused a second hit to donor lungs that already had some degree of vascular endothelial injury after undergoing EVLP. Participants in the EVLP group had an 88.9% rate of cardiopulmonary bypass use during surgery compared with 63% in the standard transplant arm. The use of ECMO to support patients after EVLP transplant in published studies ranges from 0% to 33%.[29]

The medium-term outcomes – such as number of clinical infections, lung function as measured by FEV_1 and FVC, chest radiograph appearance and numbers of rejection episodes – were comparable between the two groups. This suggests that, despite a higher rate of early PGD in the EVLP group and high rates of ECMO use, there do not appear to be other consequences of lung allograft health during the first year.

Strengths and weaknesses of the main DEVELOP-UK study

The DEVELOP-UK study has a number of strengths. It was the first study that brought together all five lung transplant centres in the UK to investigate a new technology for the benefit of patients waiting for lung transplantation. By involving all centres, the opportunity to demonstrate impact was maximised, and UK-wide policies could take account of the study. All centres were following the same protocols and using the same EVLP system to perform their assessments; this ensured the highest possible level of standardisation of the use

of the technology across the study. The level of engagement of the population of patients waiting for lung transplant surgery was an additional strength, as this enabled the opportunities to perform EVLP assessments to be maximised.

Nonetheless, there are a number of weaknesses in the study that affect our ability to draw robust conclusions. The major limitation is the fact that – due to early study termination – the small sample size in the EVLP arm limited the analyses to descriptive statistics and exploratory modelling. The other significant limitation is that the EVLP protocol used changed mid-way through the study from a hybrid protocol to the Lund protocol. This change came about following an analysis of the early safety data by the Data Monitoring Committee and based on advice received after independent safety reviews.

Challenges to study enrolment activity

As each donor lungs offer was made to a transplant centre, the lungs were assessed for suitability for standard transplantation. If they failed to satisfy criteria for standard transplantation, they were considered for EVLP assessment and reconditioning. This was possible only if there was an appropriate potential recipient for that donor organ (based on blood group, tissue typing and size matching) who had signed at least an EOI form for the study. The criteria by which the decisions to perform EVLP were made were clearly defined in the study protocol. If there was no matching recipient or no consented recipient available, then the opportunity to perform an EVLP assessment was lost to the study.

The predicted activity for EVLP assessments of 240 over the 3.5 years of the study was based on the need to enrol 102 EVLP transplants and the expected conversion rate of EVLP assessment to transplantation of approximately 40–50%. The predicted EVLP assessment rate across the study was 6.6 per month. The actual number of EVLP assessments performed in the study was, however, lower across the study sites at < 3 per month, even when allowing for R&D delays to sites opening.

There were five potential reasons for the lower level of EVLP assessment activity seen in the study. There was a learning curve for the teams in each site both with the EVLP technique and with confidence in decision-making in the first few months of performing EVLP assessments. The delays in securing R&D approvals impacted on this during the first 11 months of the study, meaning that many centres did not hit the ground running. Difficulty in recruiting appropriately skilled clinical fellows to support the study in sites meant that no dedicated clinical fellow time was available to support study activities initially. Overcautious interpretation of EVLP inclusion/exclusion criteria by on-call transplant surgeons in sites led to missed opportunities to perform EVLP on donor lungs offered but not accepted for transplant. At one centre, technical issues with the EVLP system led to a delay in recruitment because of a change of equipment and a lack of confidence by the local team, which needed to be overcome. Finally, on numerous occasions, the organ retrieval team were sent out to evaluate donor lungs for EVLP that were not initially suitable for standard transplant to discover that with some simple management the donor lungs improved to satisfy criteria for standard transplant. These were then used in the standard arm of the study. Although a limitation of the study, this does suggest that consideration could be given in future to optimising methods of retrieval of lungs for standard transplantation.

All sites performed audits of donor offer suitability for EVLP over a 1- to 2-month period in November and December 2012 and this revealed at least three missed opportunities for EVLP assessment at each site. This suggested that donor lungs suitable for EVLP were regularly available, but that the opportunities to perform EVLP were not always taken.

Low conversion rate from ex vivo lung perfusion assessment to transplant

Once EVLP assessment and reconditioning of a donor lung was performed, the decision of whether or not the lungs were used in transplantation was determined by the criteria outlined in the study protocol and listed in *Appendix 2*. The conversion rate in moving from EVLP assessment and reconditioning to EVLP

transplant was below our predicted rate of 40–50%, with 18 EVLP transplants performed from 53 EVLP assessments (34%). The number of EVLP transplants in the treatment arm of the study therefore fell behind predicted targets. The lower conversion rate was compounded by the lower than expected numbers of EVLP assessment activity. Previous single-centre publications have suggested that much higher conversion rates can be achieved, with levels of 82% reported in one large series.[32]

However, these single-centre reports can be very selective as to which donor lungs are placed on EVLP and were not driven by a study protocol that defined the lungs that should be exposed to EVLP. It is interesting that in the multicentre NOVEL study, in which selection of lungs to undergo EVLP is protocol driven, a conversion rate of 55% was reported. Furthermore, in the NOVEL study the rate of PGD grade 3 was 21% in the 42 EVLP transplants.[83]

Actions performed to increase study enrolment activity

Amendment of consent procedures

In order to reduce missed opportunities to enrol patients receiving standard lung transplants into the control group, the consent requirements of the study were changed. The investigators believed that, as the study was simply collecting clinical outcome data in this group and there were no study interventions or changes to routine care, reconsent on the day of transplant was unnecessary and dispensable. In addition, it was felt that patients who had signed the EOI form but did not sign either a consent form or consent to continue form on the night of standard transplant could be approached when conscious and fully competent post transplant to sign their consent form retrospectively and be included in the study. A substantial amendment to the study protocol was approved by the sponsor and the Research Ethics Committee to make this change to the consent arrangements.

Communication

In an attempt to increase communication between the study management team, PIs and staff in the participating sites, the following changes were made:

- The monthly investigators' teleconference was also attended by the research nurse/study co-ordinators and clinical fellows from each site, in addition to the site PIs. This allowed the wider study team to contribute to discussions on study performance, and to highlight any specific difficulties at sites to the study management team.
- The study newsletter was sent out monthly (previously was every 2 months) to update on study progress against targets. The trial managers ensured that the newsletter was passed to the wider transplant team in each site and to the donor management teams to improve engagement and also use it as a means of reminding them of communal responsibility to the study through increasing EVLP assessments of donor lungs.

Research nurses and fellows workshop

In order to support the research nurses/study co-ordinators and clinical fellows in each site, the trial management team organised a face-to-face meeting in Newcastle in March 2013 to review the study protocol, consent process, EVLP protocol and data collection. The fellows and nurses also set up a web-based discussion group to support each other with queries and comments about study-related activities.

Missed ex vivo lung perfusion opportunity audit

Initial audits of donor lung offers in the study sites after 6 months of study activity identified a number of missed opportunities to perform EVLP assessment and reconditioning of donor lungs that were not suitable for standard transplantation. The failure to perform sufficient EVLP assessments represented the greatest threat to the successful completion of the study in an acceptable time frame. The audit results provided evidence that there was a clear potential to increase EVLP assessment activity if the study EVLP inclusion

criteria were followed more carefully. A laminated, easy-to-follow sheet outlining the EVLP criteria and a flow chart for decision-making was circulated to the on-call transplant surgeons and co-ordinators. Each site was asked to prospectively audit donor offers on a regular basis and report the results of the audit back to the investigator meeting to show improvement by reducing missed opportunities.

Study site visits

Although all sites were visited by the chief investigator and trial managers as part of site initiation, another round of site visits was arranged by the chief investigator and trial manager prior to recommencement of the study with the Lund protocol to provide support to local PIs, and to allow a meeting for questions and answers about the study. This provided the opportunity to inform the wider transplant team (surgeons, physicians, co-ordinators and perfusionists) at each site about the study progress and the importance of their role in the process, as well as to address any misconceptions or misinterpretations in study criteria for EVLP assessment and reconditioning.

The role of external agency support

The DEVELOP-UK study was fortunate to receive support from a number of groups who believed this to be a very important study. The NHS commissioners provided NHS excess treatment costs and took a keen interest in the progress of the study. The study management team ensured that the commissioners were kept informed of progress in the study through newsletters, and they did get involved to stress the importance of the study to NHS trusts from whom they commission lung transplant services. In addition, NHSBT also provided support with donor data and highlighted the importance of the study in official documents. The support offered by these agencies is testimony to the importance placed on the work by the professional NHS community.

Modifications to the ex vivo lung perfusion standard operating procedure

The DEVELOP-UK study investigators recognised that the conversion rate from EVLP assessment to EVLP transplantation of just 36% was significantly lower than that reported in other small series in single centres worldwide.[29] This might reflect the nature of the donor organs being used in the DEVELOP-UK study, but could also reflect the SOP for EVLP used in the study initially. When the study protocol was first designed, the decision of the investigators was to adopt a hybrid approach containing elements of both the Toronto and Lund approaches. The use of the Vivoline system at all sites in the study did mean fixing some aspects of the SOP, such as having an open left atrium, but the consensus among the investigators was to adopt some aspects of the Toronto protocol as well with a limited flow and acellular perfusate. At the time the initial SOP was agreed, worldwide experience was substantially higher with the acellular and limited-flow approach than with a blood-based perfusion and full-flow approach.

However, after the study commenced, experience with the Vivoline EVLP system had grown worldwide and several groups (Gothenburg, Copenhagen and Brisbane) generated single-centre series with the Lund approach of full flow and red blood cell-supplemented perfusate and an open left atrium. The conversion rate from EVLP assessments to EVLP transplants using the full Lund protocol and the Vivoline system has been reported as being significantly higher, at > 80% than that which was experienced in the first stage of the DEVELOP-UK study.

In an attempt to increase EVLP transplant activity in the DEVELOP-UK study, and following advice from the independent expert review, the investigators agreed to amend the EVLP SOP to follow the Lund approach in its entirety. This was hoped to have a significant impact in converting EVLP assessments to transplants and boosting enrolment to the treatment arm of the study. The impact of such a change on patients already enrolled into the EVLP arm was discussed with the Trial Steering Committee independent statisticians. It was felt that any effect of change of SOP could be considered at the end of the study in an appropriate subanalysis. This subanalysis was performed and the findings were discussed earlier in this chapter.

Health economic analysis

The study included both a within-study assessment of costs and HRQoL, and an exploratory economic model. For the within-study data, it is obvious from the large SDs of *Tables 30–37* that there is significant variation in the cost associated with the transplant of each individual, no matter which one of the two procedures was followed. This means that there is a large variability between the lung recipients regarding the resources required in each stage of the study.

Based on the calculations made, the average total cost per recipient for the standard donor lung transplantation is equal to £59,608 (SD £42,664). Almost half of this cost (£34,109) consists of the cost of the post-operative care, which also shows the biggest variability between the patients (SD £39,561). This large difference mainly lies on the need for ECMO and the length of stay in the ITU. In the standard arm, the mean total QALYs gained per recipient were estimated to be 0.533.

As far as the EVLP lung transplant is concerned, the total cost of the transplant was estimated to be around £139,081 (SD £58,916). This high cost is partially a result of the cost of the EVLP procedure (mean cost £42,633) and partly because of the cost of the post-operative care (mean cost £56,136). The variability in the total EVLP cost is similarly high, showing that the cost of the EVLP transplant might vary up to £58,916 from the average cost per recipient. This variability is, again, because of the use of ECMO and the length of hospital stay that the recipient might require after the transplant. Finally, the total QALYs gained per EVLP recipient were estimated to be 0.527.

A regression model on cost identified three statistically significant predictors of increased total cost: higher quality of life when the person joined the waiting list; use of EVLP procedure; and transplanting two lungs rather than one lung. A sensitivity analysis excluding quality of life on joining the waiting list (because relatively few respondents completed the SF-36 at this point) gave broadly similar results, but was a much poorer fit for the model data. One value of the regression model results is that information is now available to assist researchers involved in modelling events that include lung transplantation. They now have an additional data source that can be used and tailored to the characteristics of the patients modelled.

The exploratory model-based analysis estimated an incremental cost per QALY was £73,000, well over the typical ceiling ratio adopted by NICE.

The average discounted lifetime cost for a standard lung transplant was £64,861 and £69,358 for when EVLP available. The number of discounted life-years was 5.38 for standard transplant and 5.41 in the EVLP service, the increased life-years in the EVLP service reflect the increased number of lung transplants in the EVLP service: 726 transplants in the standard service and 742 in the EVLP service. The discounted QALYs are 3.48 and 3.54 in the standard and EVLP services, respectively. The higher level of QALYs in the EVLP service reflected both the increased life-years in this service and the higher utilities in the EVLP recipients. The conclusion was broadly consistent across the range of scenarios considered. Given the novel nature of the therapy, it is not possible to put these findings into the context of other research. A comprehensive literature review identified no other cost-effectiveness studies comparing EVLP lung transplantation with standard lung transplantation.

As far as the exploratory model-based analysis is concerned, the analysis suggests that non-technical solutions to increasing the availability of lungs for transplant may be worthwhile investigating. At present, the Newcastle and Birmingham lung transplant teams are carrying out EVLP lung transplant again as part of a service evaluation. This will provide a valuable opportunity to assess whether or not the increase in standard lung transplant witnessed during the DEVELOP-UK study is replicated when EVLP is again available as a back-up for substandard lungs.

Strengths and limitations of the within-trial descriptive analysis

The economic evaluation and regression model within the DEVELOP-UK study draws upon the strengths described above. It also suffers many of the same limitations; primarily caused by the limited number of

data available on EVLP. Therefore, the within-study economic component was limited to a descriptive analysis of the available data; any comparative data are presented primarily for illustrative purposes, and thus should be treated cautiously.

In addition to the limited sample size, there was also a considerable degree of missing data in some parts of the CRF sent by certain sites, which meant that assumptions based on the data collected from the rest of the sites needed to be made. Similarly, responses were sought on the SF-36 for all participants while they were still on the waiting list, as well as after 90 days and 12 months from the date of the transplant. However, there were a considerable number of missing responses from the SF-36, which meant that robust estimates of QALYs could not be made. This same issue limited the regression model on costs. However, a model excluding quality of life that therefore included data from more study participants was a much poorer fit for the data, although it did provide similar results.

Although considerable efforts were made to capture costs over the entire patient pathway, the different administration and organisation systems between the transplant sites meant that data were not readily available to estimate the patient's travelling to the transplant centre before surgery. Consequently, these costs were considered as missing. This means that total costs were underestimated, although it was believed that these costs would make up only a small proportion of total costs.

Strengths and limitations of the exploratory analysis model

Model strengths include the following: the parameters used in the model were all based on the UK adult lung transplant population, so were generalisable to this population; ISPOR guidelines[55] were followed when designing the model, so as to reflect best practice; and uncertainty was evaluated using sensitivity analysis. Nevertheless, the limited number of data available from the DEVELOP-UK study imposes limitations on the model.

In addition to the generally limited data, a further key model limitation is that, in the model, it was assumed that when a patient in the waiting list state was removed from that state to a state 'removed from waiting list' (state G), they no longer accrued any costs or utilities. This assumption is in line with assumptions made in a Dutch economic evaluation of a lung transplant service.[84] Although the reason for removal from the waiting list is unknown, it is reasonable to assume that most patients will be removed as a result of worsening health. The impact of this is to increase average total QALYs and reduce average total costs. This in turn would improve the cost-effectiveness of the standard service relative to the service including EVLP, because for the standard service people are less likely to be transplanted in any given time period and hence are more likely to be removed from the list before a transplant.

The qualitative interview substudy

Patients' understanding and information needs regarding ex vivo lung perfusion

Generally, patients had a good understanding of what was involved in EVLP and were able to give clear explanations of what was involved. However, some patients gave confused explanations or appeared to have a limited understanding of EVLP. This may be explained by conclusions from other research, which suggests that the severity of someone's illness may affect the amount of information that they are able to retain.[85,86] Alternatively, it could be, as Lowton has argued,[69] that simple definitions such as those offered by the participants in this study may illustrate a limited understanding and lack of information. All patients were provided with the same information when taking part in a study. Long *et al.*[87] suggest that when information is being given at a very emotional time, it is difficult for patients and their families to take in all the detail, and thus that there is a need for better methods of communication to be employed. Information giving in any study is always challenging and it may be, as Entwistle *et al.*[88] have argued, that to improve everyone's understanding, key facts about the research should be given to everyone, with supplementary information available for those who request it, including links to online resources.

Reasons for participating in the DEVELOP-UK study

This qualitative substudy suggests a number of reasons why people consented to take part in the DEVELOP-UK study. First, many people interviewed appeared to think that participating in the DEVELOP-UK study might increase the likelihood of them receiving a transplantation sooner. Echoing the research of Bjørk *et al.*,[89] one of the concerns expressed by several patients was the increasing possibility that that the longer they waited the greater their chance of dying while on the transplant list. Second, people gave altruistic reasons for taking part, such as wanting to help other patients or the clinical team, in whom they had a great deal of trust. Other studies have found that trust in the clinician[90] or the notion for some that they will be the 'first to [have a] go' may be enough to override any uncertainties patients may have about a treatment.[86] As noted earlier, it is important to emphasise that, for many people, consenting to take part in the DEVELOP-UK study was not considered as significant a decision or event as actually being placed on the transplant waiting list in the first place. The emphasis placed by patients on decision to go on the transplant register ought to be reflected in the information we give patients.

Impact on everyday life of waiting for a transplant

It is recognised that any chronic condition can have a potentially 'disruptive' effect on people's lives and their own biographies,[91] and this would seem to be true for patients in this study. Waiting for a transplant involves multiple ongoing disruptions to everyday life, and has an impact not just on patients themselves, but also on others, usually their family.[92,93] Patients have to continually adjust to new routines, restrictions and, sometimes, new treatment regimes. When a patient experiences false alarms or hospital stays as a result of deterioration of their condition, their lives are further disrupted.[91] This waiting, for some, disrupts life to the extent that life is on hold, in limbo; as Naef *et al.*[93] have argued, the waiting rules their life.

Waiting for a transplant involves experiencing and balancing hope and despair, illness and good health, survival and function. For example, patients need to be sick enough to be put on the list but stay well enough for a transplant should this be offered. Initially, when they are placed on the transplant list they are filled with hope,[94] but this can often be replaced by feelings of disappointment as the wait continues and they realise that they may not get a transplant in time.[95] Patients must also manage being on the waiting list and waiting for a transplant with continuing to try to live their everyday lives and function within their families (and for some at work), all of which must be balanced alongside the deterioration of their condition and the further limitations this imposes on them.[96] The impact of deteriorating health, the experience of waiting and the possibility of dying before a transplantation may provide some insight into why people wanted to take part in the DEVELOP-UK study.

Strengths and weaknesses of interview substudy

One of the strengths of this qualitative study is that it gives a unique, detailed insight into patient views, expectations and experiences regarding EVLP specifically, and lung transplantation more generally.
The use of telephone interviews in this study enabled us to interview a diverse group of patients spread over a large geographical area. This approach to interviewing in this study appeared to be particularly successful as, given the need for patients to avoid infection and remain well enough to be able to receive a transplant, telephone interviews bore no additional risk to patients in terms of infection. Recruitment to interviews may not have been as successful if patients were required to take part in face-to-face interviews. This is something that may be of use when considering recruiting to future research with vulnerable and/or very sick patient groups.

The weaknesses of this qualitative research are twofold. First, because of the limited number of patients who underwent an EVLP transplant, there were few patients with this experience to recruit. This means that it is difficult to infer anything from the findings specifically about EVLP post-transplantation experiences. Second, the only patients available to be invited to participate in the qualitative study were those who had agreed to be part of the main trial, thus we know nothing of the reasons why people did not want to take part in the trial.

The data from this qualitative substudy provide some insights into patients' experiences, which can be used to improve future practice development in the area of transplant research and EVLP research in particular. This substudy suggests that patients had a good understanding of the need for, and processes of, EVLP, although in the future clinicians may want to consider exploring different ways and modes of providing information depending on patient preferences. Finally, this work appears to suggest that if EVLP can increase the number of suitable donor lungs available, then it is likely to be regarded as an acceptable technology to patients waiting for a lung transplant.

The DEVELOP-UK study implications for practice

The DEVELOP-UK study is the first to report poorer outcomes in a group of EVLP transplants than a contemporaneous standard lung transplant group. It is, however, the first non-commercial multicentre EVLP study performed and relied on a small number of centres (five) in a single country to aim to deliver a substantial number of EVLP assessments and subsequent transplants. To date, two commercially funded multicentre EVLP studies have been performed, but have not yet published their results other than in abstract format.[97,98]

The slow enrolment into the EVLP arm of the study was because of a combination of the low number of EVLP assessments performed, and the low conversion rate from EVLP assessment to transplant. This demonstrates the challenge of running an EVLP assessment service alongside an active clinical transplant programme, when logistics and staff availability because of competing transplant activity can significantly affect units' ability to perform EVLP assessments, even if resourced.

The higher rate of early PGD grade 3 and need for ECMO support in the EVLP arm has raised issues about the selection of the best lungs on which to perform EVLP. Although there was a much higher ECMO rate in the EVLP arm, it was not associated with a higher mortality risk in the recipients undergoing ECMO, which in most cases was limited to a few days' support. The almost uniform use of cardiopulmonary bypass in recipients of EVLP donor lungs (89%) may have also contributed to the high early PGD 3 rates and the frequent use of ECMO as a second hit to donor lungs, which already have a disrupted vascular integrity.

Finally, it appears that use of our hybrid EVLP protocol was not as effective in terms of conversion rate and possibly 1-year survival after transplant as the Lund protocol, suggesting that mixing elements of established protocols is not advisable and that matching the appropriate protocol to the appropriate EVLP circuit is an important consideration.

Overall, our main conclusion is that EVLP using a Lund protocol has the potential to offer an increased chance of achieving effective lung transplant in patients at high risk of death on the waiting list.

The DEVELOP-UK study implications for future research

After completing a study of the complexity of DEVELOP-UK, it is important that time is taken to reflect on what lessons can be learnt and how these should guide future research in this area. Although the overall findings of the DEVELOP-UK study were not what was hoped for, and did not allow the original research question to be definitively answered, there are still a significant number of factors to consider that will help to direct further research in the area of EVLP.

Study design

The decision to conduct an open, observational, non-inferiority study was made after careful consideration by the investigator group, in consultation with the HTA programme commissioning brief. However, this approach brought with it some significant challenges. The open nature of the study meant that bias was introduced to the wider clinical teams when early complications occurred. This is likely to have contributed to

poor recruitment of lungs for EVLP. It is unlikely to be possible in the future to blind investigators to which organs have been exposed to EVLP assessment and reconditioning if EVLP is conducted at all investigating sites. However, in the future, if EVLP activity was concentrated in a smaller number of more experienced sites and then organs were transported after EVLP to remote sites, this could reduce the risk of bias.

There is also the issue of what is the best research question to evaluate in a future EVLP study. It has been suggested that a better question than comparing EVLP with standard lung transplant outcomes is to compare EVLP outcomes with the risk of waiting list mortality. The difficulty with this question is that not everyone on the waiting list has access to organs in an equal way. Size, blood group and presence of pre-formed HLA antibodies can limit access to transplant opportunity in some patients, and there is also the issue that EVLP might be offered more readily to the more severely ill patients on the list to reduce their waiting time on the transplant list. To compensate for these potential confounders, it might be possible to consider a cluster-type study, with some sites acting as control centres, and others with specific experience offering EVLP.

Study logistics

The model of having dedicated EVLP centres may also be important to consider if future multicentre EVLP studies are to be successfully performed. Our experience was that one centre (Newcastle) did 50% of the EVLP assessments and 50% of the EVLP transplants, and the other four centres did not achieve their targets for recruitment of donor lungs to undergo EVLP. This suggests that expecting every transplant centre to be able to provide an EVLP service is probably unrealistic, even if appropriate resource is provided. EVLP makes an already challenging clinical situation with an emergency surgical procedure requiring huge manpower resources even more complicated. Centres enrolled in EVLP studies in the future should have previously demonstrated an ability to deliver a clinical EVLP service effectively and have performed at least 15–20 EVLP procedures before being invited to enrol in an EVLP study.

Choice of ex vivo lung perfusion protocol

There is evidence that both the Toronto and the Lund protocols can be effective at assessing and reconditioning donor lungs for transplantation. There is a different philosophy behind each protocol with real physiological differences. In the future, work should be done to help determine which elements of the protocols are critical. Our use of a hybrid approach at the start of the DEVELOP-UK study was associated with a high rate of early severe PGD and need for ECMO. The reason for this requires further investigation, particularly whether or not a combination of EVLP followed by performing transplant surgery on cardiopulmonary bypass causes a second hit, which increases vascular leak and early reperfusion injury. In addition, as all but one of the recipients who required ECMO was weaned from this support rapidly, it raises the question if this should be considered a prophylactic intervention to any recipient receiving a higher-risk donor lung after EVLP. The use of ECMO routinely intraoperatively in higher-risk recipients is increasing internationally and maybe this approach should be considered for higher-risk donor organs as well.

Identifying which donor lungs should undergo ex vivo lung perfusion

The conversion rate from EVLP assessment to transplant varies significantly in the published case series from > 90% to 40%. In the DEVELOP-UK study, only 30–40% of the donor lungs perfused satisfied transplant criteria. It is unclear if this was a problem with donor organ selection for EVLP or a result of the rigidity of following a multicentre prospective study protocol, which imposes stricter decision-making than would happen in a single centre outside a formal study setting. The conversion rate has a significant effect on overall costs of offering an EVLP service, and a target conversion rate of > 50% would seem reasonable to aim for. More work needs to be done to help identify which donor lungs can be effectively reconditioned and for which EVLP should not be considered.

In conclusion, many lessons were learnt in conducting the DEVELOP-UK study, and a future study would need to be designed differently, in order to have a better chance of hitting its recruitment targets, and of fully addressing the research question.

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Contributions of authors

Andrew Fisher (Professor of Respiratory Transplant Medicine) was the study chief investigator, designed the study, was principal applicant for funding, wrote the study protocol, supervised the overall conduct of the study, interpreted study data, and co-wrote and edited the final report.

Anders Andreasson (Clinical Research Associate in Cardiothoracic Surgery) conducted the Newcastle EVLP assessments, collected and interpreted study-wide data, and co-wrote and edited the final report.

Alexandros Chrysos (Research Associate in Health Economics) collected and interpreted study data, and co-wrote and edited the final report.

Joanne Lally (Research Associate in Qualitative Research) designed the interview study protocol, conducted participant interviews, collected and interpreted study data and co-wrote part of the final report.

Chrysovalanto Mamasoula (Research Associate in Medical Statistics) conducted the main study analysis and co-wrote part of the final report

Catherine Exley (Professor of Qualitative Health Research) was a co-applicant, secured funding, co-wrote the study protocol, interpreted study data, and co-wrote and edited the final report.

Jennifer Wilkinson (Senior Clinical Trial Manager) led the clinical trials unit teams involvement the study, co-wrote the study protocol, interpreted study data and co-wrote the final report.

Jessica Qian (Trial Manager) was responsible for day-to-day running of the study, co-ordinated communications across sites and managed study governance, and provided editorial input into the final report.

Gillian Watson (Trial Manager) was responsible for day-to-day running of the study, co-ordinated communications across sites and managed study governance, and provided editorial input into the final report.

Oli Lewington (Patient and Service User Representative) represented the views of patients in the design of the study, reviewed and edited all participant documentation, and reviewed the final report and our dissemination strategy.

Thomas Chadwick (Clinical Trials Statistician) designed the statistical plan in the study protocol, was a co-applicant for funding and led the final study statistical analysis.

Elaine McColl (Director of Newcastle Clinical Trials Unit) designed the protocol, was a co-applicant for funding, reviewed study results and edited the final report.

Mark Pearce (Professor of Applied Epidemiology) designed the protocol, was a co-applicant for funding, led the survival modelling analysis, reviewed study data and contributed to the final report.

Kay Mann (Research Associate in Clinical Epidemiology) conducted the survival modelling analysis, reviewed study results and contributed to the final report.

Nicola McMeekin (Research Assistant in Health Economics) performed part of the health economic assessment study, interpreted results and contributed to the final report.

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John Dark (Professor of Cardiothoracic Surgery) designed the protocol, was a co-applicant for funding, led study activity at his site, reviewed study results and contributed to the final report.

Data sharing statement

We shall make the study data available to the scientific community with as few restrictions as feasible, while retaining exclusive use until the publication of our major outputs. The data will be made available by contacting the corresponding author.

References

1. Office for National Statistics. *Statistical Bulletin: Deaths Registered in England and Wales (Series DR): 2012*. 2013. URL: www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsregisteredinenglandandwalesseriesdr/2013-10-22#leading-causes-of-mortality-in-2012 (accessed 29 January 2016).
2. Fisher AJ, Dark JH, Corris PA. Improving donor lung evaluation: a new approach to increase organ supply for lung transplantation. *Thorax* 1998;**53**:818–20. http://dx.doi.org/10.1136/thx.53.10.818
3. Botha P, Fisher AJ, Dark JH. Marginal lung donors: a diminishing margin of safety? *Transplantation* 2006;**82**:1273–9. http://dx.doi.org/10.1097/01.tp.0000236099.52382.74
4. Fisher AJ, Wardle J, Dark JH, Corris PA. Non-immune acute graft injury after lung transplantation and the risk of subsequent bronchiolitis obliterans syndrome (BOS). *J Heart Lung Transplant* 2002;**21**:1206–12. http://dx.doi.org/10.1016/S1053-2498(02)00450-3
5. Arcasoy SM, Fisher A, Hachem RR, Scavuzzo M, Ware LB, ISHLT Working Group on Primary Lung Graft Dysfunction. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction part V: predictors and outcomes. *J Heart Lung Transplant* 2005;**24**:1483–8. http://dx.doi.org/10.1016/j.healun.2004.11.314
6. Wallinder A, Ricksten SE, Silverborn M, Hansson C, Riise GC, Liden H, *et al.* Early results in transplantation of initially rejected donor lungs after ex vivo lung perfusion: a case-control study. *Eur J Cardiothorac Surg* 2014;**45**:40–4. http://dx.doi.org/10.1093/ejcts/ezt250
7. Korovesi I, Papadomichelakis E, Orfanos SE, Giamarellos-Bourboulis EJ, Livaditi O, Pelekanou A, *et al.* Exhaled breath condensate in mechanically ventilated brain-injured patients with no lung injury or sepsis. *Anesthesiology* 2011;**114**:1118–29. http://dx.doi.org/10.1097/ALN.0b013e31820d84db
8. Fisher AJ, Donnelly SC, Hirani N, Burdick MD, Strieter RM, Dark JH, Corris PA. Enhanced pulmonary inflammation in organ donors following fatal non-traumatic brain injury. *Lancet* 1999;**353**:1412–13. http://dx.doi.org/10.1016/S0140-6736(99)00494-8
9. Fisher AJ, Donnelly SC, Hirani N, Haslett C, Strieter RM, Dark JH, Corris PA. Elevated levels of interleukin-8 in donor lungs is associated with early graft failure after lung transplantation. *Am J Respir Crit Care Med* 2001;**163**:259–65. http://dx.doi.org/10.1164/ajrccm.163.1.2005093
10. De Perrot M, Sekine Y, Fischer S, Waddell TK, McRae K, Liu M, *et al.* Interleukin-8 release during early reperfusion predicts graft function in human lung transplantation. *Am J Respir Crit Care Med* 2002;**165**:211–15. http://dx.doi.org/10.1164/ajrccm.165.2.2011151
11. Kaneda H, Waddell TK, de Perrot M, Bai XH, Gutierrez C, Arenovich T, *et al.* Pre-implantation multiple cytokine mRNA expression analysis of donor lung grafts predicts survival after lung transplantation in humans. *Am J Transplant* 2006;**6**:544–51. http://dx.doi.org/10.1111/j.1600-6143.2005.01204.x
12. Avlonitis VS, Wigfield CH, Golledge HD, Kirby JA, Dark JH. Early hemodynamic injury during donor brain death determines the severity of primary graft dysfunction after lung transplantation. *Am J Transplant* 2007;**7**:83–90. http://dx.doi.org/10.1111/j.1600-6143.2006.01593.x
13. Avlonitis VS, Fisher AJ, Kirby JA, Dark JH. Pulmonary transplantation: the role of brain death in donor lung injury. *Transplantation* 2003;**75**:1928–33. http://dx.doi.org/10.1097/01.TP.0000066351.87480.9E

14. Okada Y, Zuo XJ, Toyoda M, Marchevsky A, Matloff JM, Oishi H, *et al.* Adenovirus mediated IL-10 gene transfer to the airway of the rat lung for prevention of lung allograft rejection. *Transpl Immunol* 2006;**16**:95–8. http://dx.doi.org/10.1016/j.trim.2006.03.012

15. Martins S, de Perrot M, Imai Y, Yamane M, Quadri SM, Segall L, *et al.* Transbronchial administration of adenoviral-mediated interleukin-10 gene to the donor improves function in a pig lung transplant model. *Gene Ther* 2004;**11**:1786–96. http://dx.doi.org/10.1038/sj.gt.3302357

16. Fischer S, Liu M, MacLean AA, de Perrot M, Ho M, Cardella JA, *et al.* In vivo transtracheal adenovirus-mediated transfer of human interleukin-10 gene to donor lungs ameliorates ischemia–reperfusion injury and improves early post-transplant graft function in the rat. *Hum Gene Ther* 2001;**12**:1513–26. http://dx.doi.org/10.1089/10430340152480249

17. Itano H, Mora BN, Zhang W, Ritter JH, McCarthy TJ, Yew NS, *et al.* Lipid-mediated ex vivo gene transfer of viral interleukin 10 in rat lung allotransplantation. *J Thorac Cardiovasc Surg* 2001;**122**:29–38. http://dx.doi.org/10.1067/mtc.2001.114636

18. Orens JB, Boehler A, de Perrot M, Estenne M, Glanville AR, Keshavjee S, *et al.* A review of lung transplant donor acceptability criteria. *J Heart Lung Transplant* 2003;**22**:1183–200. http://dx.doi.org/10.1016/S1053-2498(03)00096-2

19. Fisher AJ, Donnelly SC, Pritchard G, Dark JH, Corris PA. Objective assessment of criteria for selection of donor lungs suitable for transplantation. *Thorax* 2004;**59**:434–7. http://dx.doi.org/10.1136/thx.2003.007542

20. Ware LB, Wang Y, Fang X, Warnock M, Sakuma T, Hall TS, Matthay M. Assessment of lungs rejected for transplantation and implications for donor selection. *Lancet* 2002;**360**:619–20. http://dx.doi.org/10.1016/S0140-6736(02)09774-X

21. Jirsch DW, Fisk RL, Couves CM. Ex vivo evaluation of stored lungs. *Ann Thorac Surg* 1970;**10**:163–8. http://dx.doi.org/10.1016/S0003-4975(10)65582-8

22. Steen S, Sjöberg T, Pierre L, Liao Q, Eriksson L, Algotsson L. Transplantation of lungs from a non-heart-beating donor. *Lancet* 2001;**357**:825–9. http://dx.doi.org/10.1016/S0140-6736(00)04195-7

23. Wierup P, Haraldsson A, Nilsson F, Pierre L, Scherstén H, Silverborn M, *et al.* Ex vivo evaluation of nonacceptable donor lungs. *Ann Thorac Surg* 2006;**81**:460–6. http://dx.doi.org/10.1016/j.athoracsur.2005.08.015

24. Steen S, Ingemansson R, Eriksson L, Pierre L, Algotsson L, Wierup P, *et al.* First human transplantation of a nonacceptable donor lung after reconditioning ex vivo. *Ann Thorac Surg* 2007;**83**:2191–4. http://dx.doi.org/10.1016/j.athoracsur.2007.01.033

25. Ingemansson R, Eyjolfsson A, Mared L, Pierre L, Algotsson L, Ekmehag B, *et al.* Clinical transplantation of initially rejected donor lungs after reconditioning ex vivo. *Ann Thorac Surg* 2009;**87**:255–60. http://dx.doi.org/10.1016/j.athoracsur.2008.09.049

26. Cypel M, Rubacha M, Yeung J, Hirayama S, Torbicki K, Madonik M, *et al.* Normothermic ex vivo perfusion prevents lung injury compared to extended cold preservation for transplantation. *Am J Transplant* 2009;**9**:2262–9. http://dx.doi.org/10.1111/j.1600-6143.2009.02775.x

27. Cypel M, Yeung JC, Liu M, Anraku M, Chen F, Karolak W, *et al.* Normothermic ex vivo lung perfusion in clinical lung transplantation. *N Engl J Med* 2011;**364**:1431–40. http://dx.doi.org/10.1056/NEJMoa1014597

28. Zych B, Popov AF, Stavri G, Bashford A, Bahrami T, Amrani M, *et al.* Early outcomes of bilateral sequential single lung transplantation after ex-vivo lung evaluation and reconditioning. *J Heart Lung Transplant* 2012;**31**:274–81. http://dx.doi.org/10.1016/j.healun.2011.10.008

29. Andreasson AS, Dark JH, Fisher AJ. Ex vivo lung perfusion in clinical lung transplantation – state of the art. *Eur J Cardiothorac Surg* 2014;**46**:779–88. http://dx.doi.org/10.1093/ejcts/ezu228

30. Cypel M, Yeung JC, Machuca T, Chen M, Singer LG, Yasufuku K, *et al.* Experience with the first 50 ex vivo lung perfusions in clinical transplantation. *J Thorac Cardiovasc Surg* 2012;**144**:1200–6. http://dx.doi.org/10.1016/j.jtcvs.2012.08.009

31. Cypel M, Yeung JC, Hirayama S, Rubacha M, Fischer S, Anraku M, *et al.* Technique for prolonged normothermic ex vivo lung perfusion. *J Heart Lung Transplant* 2008;**27**:1319–25. http://dx.doi.org/10.1016/j.healun.2008.09.003

32. Cypel M, Aigner C, Sage E, Manchuca T, Slama A, Stern M, *et al.* Three center experience with clinical normothermic ex vivo lung perfusion. *J Heart Lung Transplant* 2013;**32**:S16. http://dx.doi.org/10.1016/j.healun.2013.01.021

33. Warnecke G, Moradiellos J, Tudorache I, Kühn C, Avsar M, Wiegmann B, *et al.* Normothermic perfusion of donor lungs for preservation and assessment with the Organ Care System Lung before bilateral transplantation: a pilot study of 12 patients. *Lancet* 2012;**380**:1851–8. http://dx.doi.org/10.1016/S0140-6736(12)61344-0

34. TransMedics. *International Randomized Study of the TransMedics Organ Care System (OCS Lung) for Lung Preservation and Transplantation (INSPIRE)*. 2011. URL: www.clinicaltrials.gov/ct2/show/NCT01630434 (accessed 20 April 2015).

35. TransMedics. *International EXPAND Lung Pivotal Trial (EXPANDLung).* 2013. URL: www.clinicaltrials.gov/ct2/show/NCT01963780 (accessed 20 April 2015).

36. Andreasson A, Karamanou DM, Perry JD, Perry A, Özalp F, Butt T, *et al.* The effect of ex vivo lung perfusion on microbial load in human donor lungs. *J Heart Lung Transplant* 2014;**33**:910–16. http://dx.doi.org/10.1016/j.healun.2013.12.023

37. Cypel M, Liu M, Rubacha M, Yeung JC, Hirayama S, Anraku M, *et al.* Functional repair of human donor lungs by IL-10 gene therapy. *Sci Transl Med* 2009;**1**:4–9. http://dx.doi.org/10.1126/scitranslmed.3000266

38. Lee JW, Fang X, Gupta N, Serikov V, Matthay MA. Allogeneic human mesenchymal stem cells for treatment of E. coli endotoxin-induced acute lung injury in the ex vivo perfused human lung. *Proc Natl Acad Sci USA* 2009;**106**:16357–62. http://dx.doi.org/10.1073/pnas.0907996106

39. Christie JD, Carby M, Bag R, Corris P, Hertz M, Weill D, ISHLT Working Group on Primary Lung Graft Dysfunction. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction part II: definition. A consensus statement of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2005;**24**:1454–9. http://dx.doi.org/10.1016/j.healun.2004.11.049

40. Couraud L, Nashef SA, Nicolini P, Jougon J. Classification of airway anastomotic healing. *Eur J Cardiothorac Surg* 1992;**6**:496–7. http://dx.doi.org/10.1016/1010-7940(92)90247-U

41. National Health Service. *Blood and Transplant Data on Organ Donation and Transplantation*. URL: www.odt.nhs.uk/donation/deceased-donation/donation-after-circulatory-death/ (accessed December 2015).

42. Krutsinger D, Reed RM, Blevins A, Puri V, De Oliveira NC, Zych B, *et al.* Lung transplantation from donation after cardiocirculatory death: a systematic review and meta-analysis. *J Heart Lung Transplant* 2015;**34**:675–84. http://dx.doi.org/10.1016/j.healun.2014.11.009

43. Benden C, Edwards LB, Kucheryavaya AY, Christie JD, Dipchand AI, Dobbels F, *et al.* The registry of the International Society for Heart and Lung Transplantation: sixteenth official pediatric lung and heart-lung transplantation report – 2013. International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2013;**32**:989–97. http://dx.doi.org/10.1016/j.healun.2013.08.008

44. UK Government Department of Constitutional Affairs. *Mental Capacity Act 2005 Code of Practice*. 2007. URL: www.opsi.gov.uk/acts/acts2005/related/ukpgacop_20050009_en.pdf (accessed 29 January 2016).

45. World Medical Organization. Declaration of Helsinki. *BMJ* 1996;**313**:1448–9. http://dx.doi.org/10.1136/bmj.313.7070.1448a

46. RAND Health Corporation. *The 36-Item Short Form Survey from the RAND Medical Outcomes Study*. URL: www.rand.org/health/surveys_tools/mos/mos_core_36item.html (accessed 5 November 2015).

47. OPTUM. *A Community for Measuring Health Outcomes using SF Tools*. URL: www.sf-36.org/tools/sf36.shtml (accessed 5 November 2015).

48. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ* 2002;**21**:271–92. http://dx.doi.org/10.1016/S0167-6296(01)00130-8

49. Department of Health. *NHS Reference Costs 2013/2014*. 2014. URL: www.gov.uk/government/publications/nhs-reference-costs-2013-to-2014 (accessed 27 August 2015).

50. Joint Formulary Committee. *British National Formulary (Online).* 2014. London: BMJ Group and Pharmaceutical Press. URL: www.medicinescomplete.com/mc/bnf/current/ (accessed 21 October 2014).

51. Curtis L. *Unit Costs of Health and Social Care 2014*. Canterbury: Personal Services Research Unit, University of Kent; 2014.

52. National Institute for Health Care Excellence. *Guide to the Methods of Technology Appraisal 2013. Foreword. Guidance and Guidelines*. London: NICE; 2013.

53. Information Services Division. *ISD Scotland Theatre Services*. 2014. URL: www.isdscotland.org/Health-Topics/Finance/Costs/Detailed-Tables/Theatres.asp (accessed 27 August 2015).

54. RAND Health. *36-Item Short Form Survey from the RAND Medical Outcomes Study 2015*. URL: www.rand.org/health/surveys_tools/mos/mos_core_36item.html (accessed 14 October 2015).

55. Roberts M, Russell LB, Paltiel AD, Chambers M, McEwan P, Krahn M, *et al.* Conceptualizing a model: a report of the ISPOR-SMDM modeling good research practices task force-2. *Med Decis Making* 2012;**32**:678–89. http://dx.doi.org/10.1177/0272989X12454941

56. National Heart Lung and Blood Institute. *What are the Risks of Lung Transplant?* 2011. URL: www.nhlbi.nih.gov/health/health-topics/topics/lungtxp/risks (accessed 20 June 2015).

57. International Society for Heart and Lung Transplantation. *Adult Lung Transplantation Statistics*. 2014. URL: www.ishlt.org/registries/slides.asp?slides=heartLungRegistry (accessed 21 May 2015).

58. Royal College of Surgeons. *Cardiothoracic Transplantation Audit*. 2011. URL: http://webtest.rcseng.ac.uk/surgeons/research/surgical-research/docs/uk-cardiothoracic-transplant-audit-report-2011/view (accessed 20 January 2016).

59. Siebert U, Alagoz O, Bayoumi AM, Jahn B, Owens DK, Cohen DJ, *et al.* State-transition modeling: a report of the ISPOR-SMDM modeling good research practices task force-3. *Med Decis Making* 2012;**32**:690–700. http://dx.doi.org/10.1177/0272989X12455463

60. National Institute for Health and Care Excellence. *Developing NICE Guidelines: The Manual. 7 – Incorporating Economic Evaluation*. 2014. URL: www.nice.org.uk/article/PMG20/chapter/7-Incorporating-economic-evaluation (accessed 31 May 2015).

61. NHS Blood and Transplant. *Organ Donation and Transplantation Activity Report 2011–2012*. 2013. URL: https://nhsbtmediaservices.blob.core.windows.net/organ-donation-assets/pdfs/activity_report_2011_12.pdf (accessed 21 May 2015).

62. NHS Blood and Transplant. *Annual Report on Cardiothoracic Transplantation 2013–14*. 2014. URL: www.odt.nhs.uk/pdf/organ_specific_report_cardiothoracic_2014.pdf (accessed 21 May 2015).

63. Boffini M, Ricci D, Barbero C, Bonato R, Ribezzo M, Mancuso E, *et al.* Ex vivo lung perfusion increases the pool of lung grafts: analysis of its potential and real impact on a lung transplant program. *Transplant Proc* 2013;**45**:2624–6. http://dx.doi.org/10.1016/j.transproceed.2013.08.004

64. Henriksen IS, Møller-Sørensen H, Møller CH, Zemtsovski M, Nilsson JC, Seidelin CT, *et al.* First Danish experience with ex vivo lung perfusion of donor lungs before transplantation. *Dan Med J* 2014;**61**:A4809.

65. Anyanwu AC, McGuire A, Rogers CA, Murday AJ. An economic evaluation of lung transplantation. *J Thorac Cardiovasc Surg* 2002;**123**:411–18. http://dx.doi.org/10.1067/mtc.2002.120342

66. Briggs A, Claxton K, Sculpher M. *Decision Modelling for Health Economic Evaluation*. New York, NY: Oxford University Press; 2006.

67. Kaba E, Thompson DR, Burnard P, Edwards D, Theodosopoulou E. Somebody else's heart inside me: a descriptive study of psychological problems after a heart transplantation. *Issues Ment Health Nurs* 2005;**26**:611–25. http://dx.doi.org/10.1080/01612840590959452

68. Kierans C. Narrating kidney disease: the significance of sensation and time in the employment of patient experience. *Cult Med Psychiatry* 2005;**29**:341–59. http://dx.doi.org/10.1007/s11013-005-9171-8

69. Lowton K. 'Double or quits': perceptions and management of organ transplantation by adults with cystic fibrosis. *Soc Sci Med* 2003;**56**:1355–67. http://dx.doi.org/10.1016/S0277-9536(02)00134-X

70. Lowton K, Gabe J. Life on a slippery slope: perceptions of health in adults with cystic fibrosis. *Sociol Health Illn* 2003;**25**:289–319. http://dx.doi.org/10.1111/1467-9566.00348

71. O'Grady JG, Asderakis A, Bradley R, Burnapp L, McPake DM, Perrin M, *et al.* Multidisciplinary insights into optimizing adherence after solid organ transplantation. *Transplantation* 2010;**89**:627–32. http://dx.doi.org/10.1097/TP.0b013e3181ca87b0

72. Taylor RM, Franck LS, Dhawan A, Gibson F. The stories of young people living with a liver transplant. *Qual Health Res* 2010;**20**:1076–90. http://dx.doi.org/10.1177/1049732310368405

73. Fielding N, Thomas H. Qualitative Interviewing. In Gilbert N, editor. *Researching Social Life*. 3rd edn. London: Sage; 2008. pp. 245–6.

74. Mays N, Pope C. Rigour and qualitative research. *BMJ* 1995;**311**:109–12. http://dx.doi.org/10.1136/bmj.311.6997.109

75. Glaser BG. The constant comparative method of qualitative analysis. *Soc Probl* 1965;**12**:436–445. http://dx.doi.org/10.2307/798843

76. Charmaz K. *Constructing Grounded Theory. A Practical Guide through Qualitative Analysis*. London: Sage; 2006.

77. Great Britain. *Data Protection Act 1998*. URL: www.legislation.gov.uk/ukpga/1998/29/contents (accessed 29 January 2016).

78. Gibbs G. *Qualitative Data Analysis: Explorations with NVivo*. Buckingham: Open University Press; 2002.

79. Sage E, Mussot S, Trebbia G, Puyo P, Stern M, Dartevelle P, *et al.* Lung transplantation from initially rejected donors after ex vivo lung reconditioning: the French experience. *Eur J Cardiothorac Surg* 2014;**46**:794–9. http://dx.doi.org/10.1093/ejcts/ezu245

80. Tikkanen JM, Cypel M, Machuca TN, Azad S, Binnie M, Chow CW, *et al.* Functional outcomes and quality of life after normothermic ex vivo lung perfusion lung transplantation. *J Heart Lung Transplant* 2015;**34**:547–56. http://dx.doi.org/10.1016/j.healun.2014.09.044

81. Machuca TN, Cypel M, Yeung JC, Bonato R, Zamel R, Chen M, *et al.* Protein expression profiling predicts graft performance in clinical ex vivo lung perfusion. *Ann Surg* 2015;**261**:591–7. http://dx.doi.org/10.1097/SLA.0000000000000974

82. Boffini M, Ricci D, Bonato R, Fanelli V, Attisani M, Ribezzo M, *et al.* Incidence and severity of primary graft dysfunction after lung transplantation using rejected grafts reconditioned with ex vivo lung perfusion. *Eur J Cardiothorac Surg* 2014;**46**:789–93. http://dx.doi.org/10.1093/ejcts/ezu239

83. Sanchez PG, Davis RD, D'Ovidio F, Cantu E, Weyant M, Camp P, *et al.* The NOVEL lung trial one-year outcomes. *J Heart Lung Transplant* 2014;**33**(Suppl.):71–2. http://dx.doi.org/10.1016/j.healun.2014.01.226

84. van Enckevort PJ, TenVergert EM, Bonsel GJ, Geertsma A, van der Bij W, de Boer WJ, *et al.* Technology assessment of the Dutch Lung Transplantation Program. *Int J Technol Assess Health Care* 1998;**14**:344–56. http://dx.doi.org/10.1017/S0266462300012307

85. Schaeffer MH, Krantz DS, Wichman A, Masur H, Reed E, Vinicky JK. The impact of disease severity on the informed consent process in clinical research. *Am J Med* 1996;**100**:261–8. http://dx.doi.org/10.1016/S0002-9343(97)89483-1

86. Renshaw A, Clarke A, Diver AJ, Ashcroft RE, Butler PE. Informed consent for facial transplantation. *Transpl Int* 2006;**19**:861–7. http://dx.doi.org/10.1111/j.1432-2277.2006.00358.x

87. Long T, Sque M, Payne S. Information sharing: its impact on donor and nondonor families' experiences in the hospital. *Prog Transplant* 2006;**16**:144–9. http://dx.doi.org/10.7182/prtr.16.2.l715846273q1h784

88. Entwistle VA, Carter SM, Trevena L, Flitcroft K, Irwig L, McCaffery K, Salkeld G. Communicating about screening. *BMJ* 2008;**337**:a1591.

89. Bjørk IT, Nåden D. Patients' experiences of waiting for a liver transplantation. *Nurs Inq* 2008;**15**:289–98. http://dx.doi.org/10.1111/j.1440-1800.2008.00418.x

90. Behrendt C, Gölz T, Roesler C, Bertz H, Wünsch A. What do our patients understand about their trial participation? Assessing patients' understanding of their informed consent consultation about randomised clinical trials. *J Med Ethics* 2011;**37**:74–80. http://dx.doi.org/10.1136/jme.2010.035485

91. Bury M. Chronic illness as biographical disruption. *Sociol Health Illn* 1982;**4**:167–82. http://dx.doi.org/10.1111/1467-9566.ep11339939

92. Brown J, Sorrell JH, McClaren J, Creswell JW. Waiting for a liver transplant. *Qual Health Res* 2006;**16**:119–36. http://dx.doi.org/10.1177/1049732305284011

93. Naef R, Bournes DA. The lived experience of waiting: a Parse method study. *Nurs Sci Q* 2009;**22**:141–53. http://dx.doi.org/10.1177/0894318409331932

94. Haugh KH, Salyer J. Needs of patients and families during the wait for a donor heart. *Heart Lung* 2007;**36**:319–29. http://dx.doi.org/10.1016/j.hrtlng.2006.11.003

95. Moran A, Scott A, Darbyshire P. Waiting for a kidney transplant: patients' experiences of haemodialysis therapy. *J Adv Nurs* 2011;**67**:501–9. http://dx.doi.org/10.1111/j.1365-2648.2010.05460.x

96. Littlefield C, Abbey S, Fiducia D, Cardella C, Greig P, Levy G, *et al.* Quality of life following transplantation of the heart, liver, and lungs. *Gen Hosp Psychiatry* 1996;**18**(Suppl. 6):36–47. http://dx.doi.org/10.1016/S0163-8343(96)00082-5

97. Sanchez PG, Davis RD, D'ovidio F, Weyan MJ, Camp PC, Cantu E III, Griffith BP. Normothermic ex vivo lung perfusion as an assessment of marginal donor lungs – the NOVEL Lung Trial. *J Heart Lung Transplant* 2013;**32**:S16–17. http://dx.doi.org/10.1016/j.healun.2013.01.022

98. Warnecke G, Van Raemdonck D, Kukreja J, Smith M, Loor G, Rea F, *et al.* Mid and long-term clinical results of OCS lung INSPIRE international trial. *J Heart Lung Transplant* 2016;**35**:S15–16. http://dx.doi.org/10.1016/j.healun.2016.01.042

99. The Newcastle upon Tyne Hospitals NHS Foundation Trust. *Annual Report & Accounts 2012/13*. URL: www.newcastle-hospitals.org.uk/downloads/Performance%20information/2012-13_NuTH_Statutory_Report_part7.pdf (accessed 6 September 2016).

100. NHS Business Service Authority. *Amendments to the Drug Tariff*. 2015. URL: www.nhsbsa.nhs.uk/PrescriptionServices/Documents/PPD%20Drug%20Tariff/June_2015.pdf (accessed 6 September 2016).

101. XVIVO Perfusion. *Homepage*. URL: www.xvivoperfusion.com/ (accessed 6 September 2016).

102. ISD Scotland. *About ISD*. URL: www.isdscotland.org/ (accessed 6 September 2016).

103. Fisher AJ. *A Study of Donor Ex-Vivo Lung Perfusion in UK Lung Transplantation*. 2013. URL: www.nets.nihr.ac.uk/__data/assets/pdf_file/0006/55770/PRO-10-82-01.pdf (accessed 6 September 2016).

Appendix 1 Couraud *et al.*'s classification of anastomotic healing

The grades corresponding to Couraud *et al.*'s classification[40] of anastomotic healing are:

- 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 2 Standard operating procedures

Ex-Vivo Lung Perfusion (EVLP)

Standard Operating Procedure (Version 3.0: 5th July 2013)

Location:

EVLP is 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:

- **Vivoline evaluation unit**: An integrated roller pump (Jostra), heater cooler unit, gas system, monitor and control unit with associated software package.
- **Vivoline disposable lung set**: Includes an oxygenator (Capiox), LDF leukocyte filter, pressure sensors and temperature probes.
- **93% Nitrogen and 7% CO2 gas mixture cylinder on a trolley**: A full cylinder contains 10000 litres and each EVLP run requires at least 2000 litres of gas mixture (3 hours).
- **Oxygen supply**: From the wall outlet.
- **ICU standard ventilator:** Model that measures minute and tidal volumes, lung compliance / resistance and airway pressure.
- Arterial blood gas machine.
- **Standard thoracic surgical instrument tray**.
- **Sterilised bronchoscope**: With suction tubing and lavage traps, 5, 10 and 20ml syringes.
- **Sample collection disposables:** Includes Duet-stapler devices for lung biopsies, specimen pots for tissue, test tubes for perfusate and ice bucket or refrigerator for sample storage (please refer to sample SOP).

Medications:

- **Saline 0.9%:** 240mls for 2xBAL and additional 100mls for flushing pressure transducers.
- **Steen Solution:** At least 4 x 500ml bottles.
- **Packed Red Blood Cells:** Request 3 packs of red blood cells from the blood bank, either universal donor (O negative) if >1 potential recipient identified or cross matched to the single known recipient.
- **THAM/TRIS solution:** Use a preparation containing Trometamol 3.0mmol/ml in a quantity as directed by base deficit to a Base Excess +/- 3 and pH of 7.35 – 7.45 (see Appendix 1).
- **Heparin:** 10,000IU unfractionated.
- **Methylprednisolone:** 500mg.
- **Antibiotics:** Meropenem 500mg is the default antibiotic if there is no documented recipient allergy to ß- lactams. If donor airway cultures known, other antibiotics can be used after discussion with microbiology.
- **Amphotericin B:** 10 mg for injection (Amphocin, Fungizone or equivalent).
- **Actrapid Insulin and 10% Glucose Solution:** Possible requirement for 10ml of 10% Glucose solution and 20 IU Actrapid Insulin but not routinely used.

Priming the Circuit:

- Connect the disposable kit to the evaluation unit according to user manual instructions.
- Flush the pressure transducers.
- Connect the water to the heater-cooler unit, open the water bag.
- Start the ***priming phase*** on the screen. Check the oxygenator for leakage.

- Calibrate the pressure transducers.
- Fill the system with 2.0L Steen solution (4 x 500ml bottles).
- Calibrate the pump occlusion by following the screen instructions.
- Recirculate perfusate at 15°C set flow to 2.0 L/minute and maximum perfusion pressure at 10 mmHg.
- Connect the gases.
- Add 10,000IU of unfractionated Heparin to circulating Steen solution.
- Add 1-2 units of Packed Red Blood Cells.
- Prepare 500mg dose of Methylprednisolone.
- Make up Antibiotics and Amphotericin B according to manufacturers' instructions.
- Add Methylprednisolone, Antibiotics and Amphotericin B to the circulating perfusate.
- Do a perfusate blood gas analysis and correct the base deficit with THAM to a Base Excess +/- 3 and pH of
  7.35 – 7.45. Add 3 mmol THAM per minus unit in base deficit please see Appendix 1.

  The blood gas needs to be temperature corrected for 15^{O}C.
- Note haematocrit of perfusate on blood gas. Target is 10-15% so add more red cells if needed.
- Check perfusate glucose and potassium concentration via blood gas analysis; if glucose <5 or >20 mmol or potassium >7mmol correct with Insulin as per Appendix 2.
- Repeat the perfusate gas prior to connecting the lung for any further corrections.
- The perfusate, pharmaceuticals and gases should be circulated for ≥15 minutes before connecting the lung.
- If satisfactory, start the ***reconditioning phase***.

Reconditioning Phase:

- Surgical dissection is performed to allow placement of the donor lung onto the Vivoline EVLP circuit in the covered organ bath to maintain humidity.
- Before connecting the lung to the circuit, take ***Lung Biopsy #1*** from the RML or Lingula and collect ***Perfusate Sample P0*** (See separate Sample collection SOP).
- Cannulate the main pulmonary artery with the quick-fix pre-fashioned cannula and open the shunt to the inflow cannula.
- The left atrium is left open and visualised to ensure a smooth flow of perfusate.
- The LA temperature probe and sampling line is secured in place equal distance from the 4 pulmonary veins.
- Where possible the trachea remains clamped with lungs partially inflated with 50% FiO2 while the quick-fix ventilation tube is secured in place. This prevents collapse of the lungs and development of atelectasis prior to the ventilation.
- Set the pulmonary artery (PA) pressure to a maximum of 15 mmHg.
- Perform de-airing of the circuit with the shunt open at a flow of 0.5L / minute for approximately 2 minutes until fully de-aired. Leave the shunt open.
- Set temperature to 32^{O}C. The system will warm up the lung automatically with a maximum delta temperature of less than 8°C.
- If initial perfusion is uneventful, increase the PA pressure limit to 20 mmHg and flow to maximum.
- The recommended max flow is 70 ml/kg IBW /minute (see Appendix 3). With a cold lung the pressure will limit the flow, when the resistance in the lung goes down the flow will increase over time.
- When temperature has reached 25^{O}C close the shunt.
- At 32^{O}C remove the clamp on the trachea and before commencing ventilation, perform a

bronchoscopy and collect ***BAL sample #1*** from either RLL or LLL using 120 ml 0.9% NaCl with the bronchoscope in a wedged position (See separate Sample collection SOP).

- Commence mechanical volume-controlled ventilation at 32^{O}C with a protective ventilation strategy:
  - Set inspired oxygen (FiO_2) to 0.5 (50%)
  - Set respiratory rate (RR) initially to 5 or 8 breaths/min according to donor IBW (see Appendix 4)
  - Set Minute volume (mV) initially to 1 L/min
  - Set PEEP at 5cmH_2O
  - Set I:E ratio 1:2 and inspiratory pause at 10%
  - Keep peak airway pressure <20 cmH_2O
- Increase temperature from 32^{O}C to 37^{O}C.
- Increase the mV in 1 L/min increments gradually as lung warms to 37^{O}C; **mV should not exceed 1.5X the flow**. Continue to keep peak airway pressure (Paw) < 20 cmH_2O. Increase the RR, as mV increases, up to a maximum of 15 breaths/min to keep tidal volume <7ml/kg IBW (see Appendix 4).
- At 32°C the perfusate flow is usually lower than the set value, please note the flow as the lungs warm to 37°C as the **minute volume should not exceed 1.5X the flow**.
- If uneventful and once 37°C reached, mV can be increased **gradually** up to a maximum of 100ml/kg IBW/ min but the tidal volume should not exceed 7ml/kg IBW (see Appendix 4).
- If persistent atelectasis present, perform a recruitment manoeuvre by transiently increasing PEEP from 5cmH_2O in increments of 1cmH_2O for a few breaths to a max of 12cmH_2O while always keeping Paw <25cmH_2O. Note flow will fall significantly during increase in PEEP. After recruitment return PEEP to 5cmH_2O.
- Flow, PVR, Lung Compliance and PA pressure to be documented once lungs reach 37°C and flow stabilised.
- Once lungs are at 37°C with stable flow and ventilation settings and satisfactory appearance, shift to the ***evaluation phase***.

Evaluation Phase:

- Once re-warming is complete and target perfusion established, the function of the donor lungs undergoing EVLP can be assessed as specified in the study protocol.
- Disconnect the oxygen from the perfusion system prior to evaluation.
- Once the perfusate is deoxygenated and confirmed on blood gas analysis, perform recruitment manoeuvres as above and set the ventilator for evaluation as below:
  - Increase FiO_2 via the ventilator from 50% to 100%.
  - PEEP can be increased to 8cmH_2O for a short period.
  - Maximum mV should not exceed 100mls/kg/min (donor IBW)
  - Keep peak airway pressure Paw <25cmH_2O
- RR can be adjusted between 12 and 15breaths/min to maintain V_T up to a maximum of 7ml/kg (donor IBW)
- Perform blood gas analysis 15 minutes after FiO_2 is increased to 100% to assess venous and arterial pO_2 values. Blood gas analyses should be performed from each pulmonary vein as well as a mixed LA sample.
- Flow, PVR, Lung Compliance and PA pressure should be carefully documented on the data sheets.
- Perform a lung deflation test by disconnecting the tracheal tube at the end of inspiration. **Remember to first reduce perfusate flow to maximum of 1.5L/min to avoid alveolar**

oedema. Recoil of the lungs is evaluated subjectively; global collapse of the lungs is defined as normal.

- If transplant suitability criteria have been achieved, move immediately to ***cooling phase*** for organ preservation.
- If transplant suitability criteria have not been achieved, return to the reconditioning phase.
- Perform hourly clinical assessments as documented in the protocol until a decision on suitability of the lungs for transplantation or 240 minutes of EVLP perfusion has been reached (from the time of reaching 37°C).
- During perfusion if pH <7.35 administer additional THAM to the Steen Solution™.
- During perfusion do not automatically replace Steen Solution™.

Cooling Phase:

- Reduce mV by a 30% reduction in tidal volume and lowering respiratory rate to 8 breaths/min
- Set temperature to 32°C
- Reconnect the oxygen to the perfusate.
- Before discontinuing ventilation, perform a bronchoscopy and collect ***BAL sample #2*** from the same lobe, but from a different segment than BAL sample #1, using 120 ml 0.9% NaCl with the bronchoscope in a wedged position (See separate Sample collection SOP).
- Stop ventilation at 32°C, clamp trachea with lungs partially inflated with 50% FiO2.
- Set temperature to 12°C and continue to cool lungs until perfusate temperature 12°C.
- Collect ***Perfusate Sample PX***.
- Disconnect PA cannula and plug PA with special bung.
- Once perfusion has stopped and the lung is disconnected, take ***Lung Biopsy #2*** from the same lobe as Lung Biopsy #1 (See separate Sample collection SOP).
- Commence topical cooling.
- Place mat under lungs and wrap towels over lungs so that they touch the mat all around lungs.
- Connect the Y shaped hose from the cooling assembly to the lung perfusion quick connection and cover the highest point of each lung. Connect the remaining hose from the cooling assembly to the shunt quick connection and place over the trachea and PA.
- In the preservation phase set pump to 2.5 L/ min. Check fluid level and add more Steen Solution if necessary.
- Maintain the lungs in topical Steen solution at 6 - 8 °C on the circuit (preservation phase) until ready for transplant.

Adaption for Single lung Reconditioning

- For cannulation, if feasible staple the contralateral PA (right PA if it is a left lung transplant or vice versa) at least 2 cm above its first branch to facilitate as much length as possible. If the pulmonary artery is too short and/or the surgeon is unable to fit the quick-fix pre-fashioned cannula, use a part of the donor's aorta to augment the cuff.
- For connection of the bronchus, please note there are 3 sizes of connection available in the disposable kit to aid achieving an effective connection. If it is a right lung EVLP, staple the left main bronchus at the level of the carina and cannulate the trachea. If it is a left lung EVLP, the left main bronchus from the level of the carina should be long enough to facilitate attachment. Ensure a seal that prevents either ineffective ventilation of fluid entering the airway.
- Set to 50% target flow i.e. 35 ml/kg body weight/minute.
- When starting ventilation, start at a minute volume of 0.5 L/min and increase to a

maximum of 1.5 times the perfusate flow.

Appendices:

Appendix A

Use of THAM/TRIS to buffer Steen Solution: THAM is available in various dilutions (ranging from 3.6% (Abbott, Köhler) to 36.5% (Braun) or 40% (Fresenius-Kabi or Addex-THAM) so caution is advised in measuring the correct amount. **PLEASE CHECK THE CONCENTRATION OF YOUR THAM PREPARATION!**

A 3.6% solution of THAM contains a concentration of Trometamol (active ingredient) of 0.33mmol/ml A 40% solution of THAM contains a concentration of Trometamol (active ingredient) of 3.0mmol/ml When buffering Steen solution in the circuit use 3mmol of THAM per minus unit in base deficit.

This will be 1ml per minus unit base deficit for the 40% THAM preparations and 10ml per minus unit base deficit if the 3.6% THAM preparation is used.

A THAM preparation of between 3.0 – 3.3 mmol/ml is strongly recommended and use of lower concentrations strongly discouraged due to the dilutional effects on Steen Solution of adding large volumes of a lower concentration THAM.

Appendix B

During perfusion administer 10ml of 10% Glucose if the perfusate glucose concentration falls below 5mmol/L. If the glucose concentration is above 20mmol/L then add 10 IU Actrapid Insulin to perfusate. Recheck glucose 5 min after any intervention. If potassium is >7mmol then administer 10 IU Actrapid Insulin and recheck potassium and glucose 5 min after intervention.

Appendix C

The ideal body weight calculation formulae used to determine the tidal volumes in protective lung ventilation are:

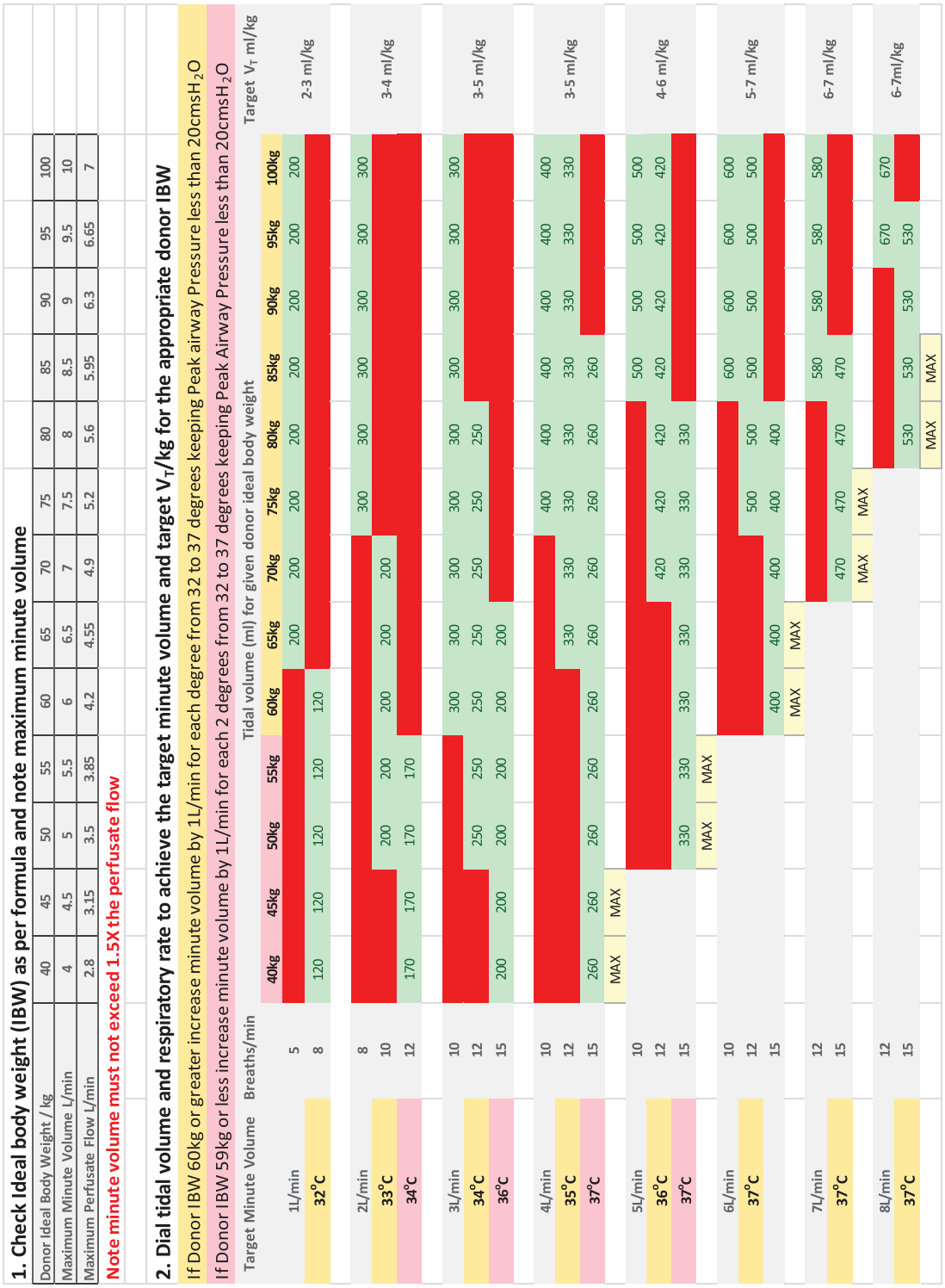
IBW (kg) for men = [(height (cm) -154) x 0.9] + 50

IBW (kg) for women = [(height (cm) -154) x 0.9] + 45.5

If you copy/paste below link you'll get an online IBW calculator

http://www.ukmicentral.nhs.uk/resource/calcs/ibw.asp?group=m

Appendix D - Ventilation strategy see chart below



1. Check Ideal body weight (IBW) as per formula and note maximum minute volume

Donor Ideal Body Weight / kg	40	45	50	55	60	65	70	75	80	85	90	95	100
Maximum Minute Volume L/min	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5	9	9.5	10
Maximum Perfusate Flow L/min	2.8	3.15	3.5	3.85	4.2	4.55	4.9	5.2	5.6	5.95	6.3	6.65	7

Note minute volume must not exceed 1.5X the perfusate flow

2. Dial tidal volume and respiratory rate to achieve the target minute volume and target V_T/kg for the appropriate donor IBW

If Donor IBW 60kg or greater increase minute volume by 1L/min for each degree from 32 to 37 degrees keeping Peak airway Pressure less than 20cmsH_2O

If Donor IBW 59kg or less increase minute volume by 1L/min for each 2 degrees from 32 to 37 degrees keeping Peak Airway Pressure less than 20cmsH_2O

Target Minute Volume	Breaths/min	Tidal volume (ml) for given donor ideal body weight													Target V_T ml/kg
		40kg	45kg	50kg	55kg	60kg	65kg	70kg	75kg	80kg	85kg	90kg	95kg	100kg	
1L/min	5	120	120	120	120	120	200	200	200	200	200	200	200	200	2-3 ml/kg
32°C	8	120	120	120	120	120	200	200	200	200	200	200	200	200	
2L/min	8							300	300	300	300	300	300	300	3-4 ml/kg
33°C	10			200	200	200	200	200	300	300	300	300	300	300	
34°C	12	170	170	170	170										
3L/min	10					300	300	300	300	300	300	300	300	300	3-5 ml/kg
34°C	12		250	250	250	250	250	250	250	250					
36°C	15	200	200	200	200	200	200								
4L/min	10							400	400	400	400	400	400	400	3-5 ml/kg
35°C	12					330	330	330	330	330	330	330	330	330	
37°C	15	260	260	260	260	260	260	260	260	260	260				
		MAX	MAX												
5L/min	10									500	500	500	500	500	4-6 ml/kg
36°C	12						420	420	420	420	420	420	420	420	
37°C	15			330	330	330	330	330	330	330					
		MAX	MAX												
6L/min	10								500	500	500	500	500	500	5-7 ml/kg
37°C	12					400	400	400	400	400					
	15					MAX	MAX								
7L/min	12										580	580	580	580	6-7 ml/kg
37°C	15						470	470	470	470					
							MAX	MAX							
8L/min	12											670	670	670	6-7ml/kg
37°C	15									530	530	530	530		
										MAX	MAX				

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DEVELOP-UK

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

RECIPIENT INCLUSION / EXCLUSION CRITERIA

Inclusion Criteria

- 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 in EVLP treatment group 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. Patients in standard control group are not required to re-confirm informed consent on the day of transplant if they have signed the Expression of Interest Form or the Informed Consent Form prior to the transplant.***

Exclusion Criteria

- 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 in EVLP treatment group 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.***

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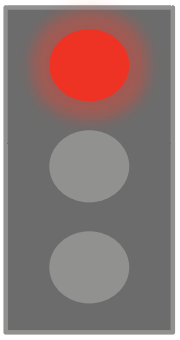
ABSOLUTE CONTRA-INDICATIONS TO DONOR ORGAN USE FOR TRANSPLANT (BASED ON NHS BT GUIDELINES)

Donation after Brain Death (DBD)



- 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***

Donation after Cardiac Death (DCD) (NHSBT Guidelines)

- As above but age >80 years

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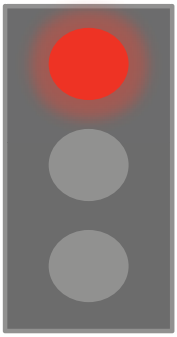
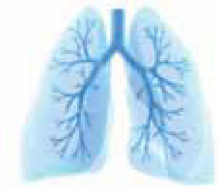
ABSOLUTE CONTRA-INDICATIONS TO DONOR LUNG USE FOR STANDARD TRANSPLANT OR FOR EVLP



- 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)



DONOR LUNG PROCUREMENT FOR ALL LUNGS

The standard lung procurement procedure will be followed for donor lungs to be used for EVLP.

- Flush the organs ante-gradely with supplemented (3.6% THAM 3.3 mls, 0.6 ml CaCl +/- 2.5 mls Prostacyclin / litre) Perfadex®:
  - the first 1 litre at room temperature,
  - the rest at 4°C. Give a minimum volume of 60ml/Kg.
- After the antegrade dose, give 200 ml 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.

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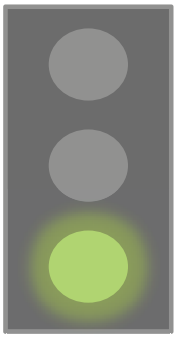
CRITERIA FOR STANDARD TRANSPLANT
(DBD AND DCD DONOR LUNGS)



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

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CRITERIA FOR EVLP ASSESSMENT AND RECONDITIONING (DBD AND DCD LUNGS)

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 >10-12 hrs and prevent donor organ use, such as:
  - Viral studies awaited
  - HLA compatibility studies
  - Pathology assessment of indeterminate mass in any donor
  - Awaiting recipient admission

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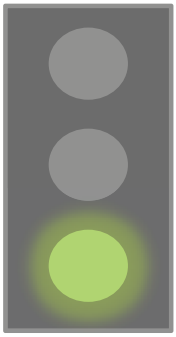
CRITERIA FOR TRANSPLANT AFTER SUCCESSFUL EVLP ASSESSMENT AND RECONDITIONING



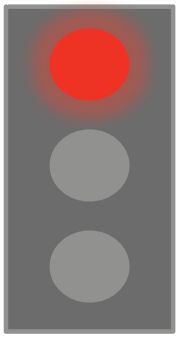
- Any DBD or DCD donor lungs meeting previously stated criteria for standard transplant
- Pulmonary artery pressure < or equal to 20 mmHg, whilst achieving stable perfusate flow of up to 70 ml/kg IBW /minute at 37°C.
- Peak airway pressure < 25 cms H_2O while achieving adequate ventilation (tidal volumes up to a max 7 mls/kg IBW)
- Oxygen capacity shown by deltaPO_2 of > 40 kPa (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 Informed Consent Form was signed on the day of transplant re-confirming consent is not required***

CRITERIA FOR FAILED EVLP ASSESSMENT AND RECONDITIONING

Transplant will not proceed if:

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



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REPORTING OF SERIOUS ADVERSE EVENTS

PROTOCOL SPECIFICATIONS

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

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***Disclaimer:* The purpose of this flyer is to act as an aid memoir and in no way replaces the trial protocol. Please refer to the main protocol for further information. The protocol may be revised periodically. If so participating centres will be informed.**

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Sample collection, processing and storage

Standard Operating Procedure

Give each sample a **unique identifying code** comprising the following: **Centre / EVLP number / Type of Sample and number / Date (DDMMYY)**

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

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.

Collection and storage of biological samples from donor lungs is limited to those donor lungs exposed to EVLP assessment and reconditioning and no samples are collected from standard donor lungs.

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Equipment:

Equipment and Reagents	***Procedure***
Sterile normal saline (0.9% NaCL solution)	**BAL, BIO**
Crushed Ice	**BAL, BIO**
Sterile universal containers	**BAL, PER**
Sterile gauze	**BAL, BIO**
Centrifuge (refrigerated if possible)	**BAL, PER**
PBS (phosphate buffered saline)	**BAL**
Improved Neubauer Haemocytometer 0.1 mm depth	**BAL**
Cytospin with Cytospin funnels and glass slides	**BAL**
1ml Storage tubes (NUNC)	**BAL, PER**
-20ºC freezer	**BAL, PER**
-80ºC freezer	
Covidien Duet (absorbable buttressed) endo-GIA stapler	**BIO**
Sample pots	**BIO**
Liquid nitrogen in Dewar storage flask	**BIO**
Formalin	**BIO**
Glutaraldehyde (see Appendix 1)	**BIO**
Dulbeccos Phosphate buffered saline. (Sigma D5773)	**BAL**
Acetone (VWR 20066.321)	**BAL**
Virkon (Du Pont)	**BAL**
Trigene (Medichem)	**BAL**
RNA later	**BAL**

BAL- BAL collection and processing

PER- Perfusate collection and processing

BIO- Donor Lung Biopsy collection and processing

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Bronchoalveolar Lavage (BAL)

BAL Collection:

- Under flexible bronchoscopic guidance perform a standardised BAL using **120 mls** of **sterile normal saline (0.9% NaCl solution)** from: Either the left or right lower lobe of the donor lung on two occasions (BAL1 and BAL2).
- Perform **BAL2** in a different segment from the same lobe as **BAL1**
- The timing of each BAL is detailed below:
  - **BAL1**: At the beginning of the EVLP process after perfusion has commenced and the lung temperature has reached at least 30°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 **BAL1** and **BAL2** record data on sample collection data sheet for:
  - the duration of perfusion before the sample is taken
  - the lobe and segment the BAL is performed in
  - the volume of saline administered
  - the volume retrieved
  - the volume after filtration
- Store **BAL1** on ice until **BAL 2** is performed and placed on ice. The 2 BAL samples can then be processed together at the end of the EVLP run.
- The samples after processing can be placed straight into a -80°C freezer if accessible. If not immediately accessible the samples can be placed at -20°C until transfer to the -80 within the following 48 hours.

BAL Processing:

- Place a minimum of 2mls to a maximum of 5mls of the total BAL sample into a sterile container and send to your hospital laboratory for gram stain and formal microbiological assessment.
- Keep the remaining BAL on ice until ready to process, this should be started as soon as is feasible and ideally within 6-8 hours of it being taken.
- Filter the BAL fluid through a single layer of gauze to remove excess mucus. The gauze can be moistened with sterile saline to aid adherence to the funnel. Measure and record the volume on the work sheet.
- Centrifuge to separate the cellular component from the acellular supernatant at 180g for 6 minutes at 4°C

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- Decant the supernatant into a clean tube, taking care not to disturb the cell pellet.
- Centrifuge the supernatant at 700g for 6 minutes at 4°C.
- Divide the supernatant into 1ml aliquots (maximum 12 from each BAL sample) and freeze at -20°C before transfer to -80°C the next working day for long term storage.
- Add Dulbeccos Phosphate Buffered Saline* (D-PBS) to the **cell pellet** to produce an opaque suspension. Mix gently.

  *(*The choice of the initial volume of D-PBS added to the pellet comes with experience and depends on the volume and visual characteristic of the starting BAL sample and the size of the cell pellet. For example a 10ml BAL sample which appears dense and opaque suggests a high cellularity sample, so in this scenario start with 10mls of Dulbeccos PBS added. If the BAL is 10ml but clear and translucent suggesting a lower cellularity sample, add just 5mls of D-PBS initially. In essence the initial volume added is a best guess and the final volume can then be adjusted to get the correct final cell concentration.)*

- To find the total cell concentration, use an Improved Neubauer counting chamber (depth 0.1mm). Count the cells in 4 large squares. (4 mm^2).
- Divide this figure by 4 then adjust the volume to give a final cell concentration of 0.5 million cells per ml.

$$\frac{\text{Total number of cells} \times 10^6}{0.5} = \text{x ml DPBS}$$

- Use the diluted cell suspension to prepare cytospins x 6, 100ul per cytospin at 300 rpm (9g) for 3 minutes. Check the quality of the cytospins microscopically. If they are too dense repeat using a more dilute cell suspension. If the cytospins are too sparse increase the volume to 150ul.
- Fix 1 cytospin in acetone at room temperature for 10 minutes then air dry.
- The remaining 5 cytospins should be air-dried and then wrapped in foil and placed in the freezer. These can be stored at -20°C before transfer to -80°C the next working day.
- Stain with Geimsa (or Diff Quick) and perform a differential count. (This can be done the next day if necessary). Perform differential cell count to determine the percentage of:
  - Neutrophils; macrophages; lymphocytes; eosinophils and epithelial cells
- Once the quality of the cytospins has been assessed the cell suspension is centrifuged at 180g for 6 minutes at 4°C. Decant the supernatant from the cell pellet and resuspend in 2mls of RNAlater. This concentrated cell suspension can then be divided to give approx 3 x 10^6 cells per tube. Snap Freeze and store at -20°C before transfer to -80°C.
- Place used cytofunnels in 1% Virkon for sterilisation. Discard all pipettes, tubes etc to clinical waste. Sterilise work surfaces with 1:50 Trigene.

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Perfusate

Perfusate Collection:

Collect samples of perfusate solution longitudinally during the EVLP process from the perfusate sampling port on the back of the Vivoline machine.

Place collected perfusate samples in an ice filled insulated box to keep at 4°C.

- Collect 5mls 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

Perfusate Processing:

- The perfusate samples can be stored on ice for the duration of the EVLP run and then placed in a fridge at 4°C until processed.
- The samples should be processed all together at the end of the EVLP run and ideally within 8 hours of collection.
- Centrifuge the perfusate samples at 180g for 6 minutes at 4°C to remove cellular debris
- If a refrigerated centrifuge is not available please keep the samples on ice immediately before and after centrifugation.
- Carefully remove the supernatant and aliquot equally into 5x1ml tubes for each time point sample before freezing at -20°C.
- Transfer them to -80°C as soon as feasible. The next working day ideally but within the following 48 hours for longer term storage.

Donor Lung Biopsy

Biopsy Collection

Take small biopsies of lung tissue using a Covidien Duet (absorbable buttressed) endo-GIA stapler from either the right middle lobe or lingular at two time points:

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  - **Biopsy 1**: Taken prior to the commencement of the EVLP process at the recipient hospital
  - **Biopsy 2**: Taken at the end of the EVLP process once perfusion has stopped
- Place biopsies on sterile gauze.
- Dampen them with 0.9% Saline in a sample pot.
- Store the pot on ice until processing.
- It is understood that there will be different storage times on ice for the two biopsies. Once cooled to 4 degrees it is unlikely to affect the cellular processes in the tissue.
- At the end of the EVLP run both biopsies can be processed at the same time. It is important is to make sure the first biopsy is kept moist in the pot but not wet.

Biopsy Processing

From each of these biopsies:

- Fix a small amount of tissue in glutaraldehyde for electron microscopy studies.
  - See detailed protocol below
- Snap freeze small amount of tissue in liquid nitrogen for subsequent mechanistic studies.
  - See detailed protocol below
- Place the remaining tissue in Formalin fixative pots.
- Sterilise the work area with 1:50 Trigene. Dispose of gloves, apron etc to clinical waste.
- Transfer Formalin fixed blocks to Pathology for paraffin (FFPE) embedding as soon as possible.
- Subsequently cut FFPE sections for routine histological evaluation (Haematoxylin and Eosin staining).

Snap freezing Procedure

- 2-3 small pieces of tissue should be prepared for freezing. Each piece should be ideally 5-10mm in diameter.
- Store biopsies / blocks at 4^{o}C until ready to be quenched.
- In a Dewar flask collect 1litre of liquid nitrogen.
- Place approx 60ml isopentane* in a plastic beaker and gently suspend in the flask of nitrogen, leave until the isopentane is almost solid, approx 10 – 15 mins.
- Remove the beaker from the Dewar flask.
- The isopentane should now be a half liquid / half frozen slurry. Place the pieces of tissue on squares of tin foil approx 1.5 x 1.5 cms using medium forceps plunge the tin foil and

tissue into the isopentane moving it through the liquid phase for approx. 30 seconds until the tissue is solid. Repeat this for each piece of tissue.

- Remove the frozen block from the isopentane and drain off any liquid then securely wrap in a 5cm square of tin foil to exclude all air. Place the wrapped tissue in a labeled unicassette, seal and plunge into the liquid nitrogen.
- Using tongs transfer the unicassette to the –20°C freezer for later transfer to –80°C storage on the next working day.
- Place all instruments in 1:50 Trigene for sterilization.
- Transfer the Dewar flask containing the Liquid nitrogen to the fume hood. Attach the hazard label and allow the nitrogen to evaporate.

(Snap freezing in isopentane slurry is considered the best methods to avoid freezing artefact. As the frozen tissue will be used mainly for cell biology purposes. The isopentane step is not compulsory part of the protocol but is recommended.)*

Preparation of lung biopsy for Electronic Microscopy (EM) examination

- 3-4 small pieces of approximately 4x4x10 mm are CAREFULLY (try not to squash) taken with a sharp scalpel or scissors from the removed lung tissue. Take these away from the stapled edges where there might be crush artefact.
- Place IMMEDIATELY in glutaraldehyde fixative as delays will lead to artefact which can be interpreted as tissue injury.
- Gently without squeezing the tissue push to the bottom of the fixative and agitate to try to get the air out of the lung. Residual air will make the tissue float and not fix resulting in artefact.
- Agitate the closed bottle to try to remove further air.
- Once the sample is adequately placed in glutaraldehyde it can be stored in the fridge until posted away for processing in Birmingham on the next convenient working day.
- See Appendix 1 for method to prepare glutaraldehyde stock solution. This is best done by an experienced pathology lab.

Appendix 1: Method for the preparation of a standard 2.5% glutaraldehyde fixative in 0.1M sodium phosphate buffer - for electron microscopy.

Contains a **Hazardous** chemical, read COSHH data sheet before preparing fixative for the first time. This is best done in an experienced pathology laboratory.

Materials and Equipment:

pH meter
Balance

Study Card Version 3.0, July 2013

500ml measuring cylinder
100ml measuring cylinder
Gloves
Clean 500ml bottles with well-fitting stoppers

Chemical Suppliers: *Glutaraldehyde EM grade (25%) Catalogue no. R1011*

Agar Scientific Ltd
Unit 7, M11 Business Link, Parsonage Lane,
Stansted, Essex, CM24 8GF
Tel: [redacted]
Email: [redacted]

di-Sodium hydrogen orthophosphate
Sodium di-hydrogen orthophosphate

VWR International Ltd.
Hunter Boulevard
Magna Park
Lutterworth
LE17 4XN
Customer service centre: [redacted]

Procedure:

Preparation of 0.2M sodium phosphate buffer

To make up stock solutions

Acidic solution (A): 31.2g/l sodium di-hydrogen orthophosphate is an 0.2M solution

Weigh out 15.6g of A; put powder in 500ml measuring cylinder, half fill with distilled water, shake until dissolved and top up to 500ml. Transfer to a clean 500ml bottle and stopper tightly. Label with 3 months expiry date.

Basic solution (B): 28.4g/l di-Sodium hydrogen orthophosphate is an 0.2M solution

Weigh out 14.2g of B. Prepare and label 'Solution B' as above.

To make up 0.2M phosphate buffer

To make 100ml of 0.2M sodium phosphate buffer measure out 23mls of solution A and 77mls of solution B in to a beaker. Mix thoroughly. This should give a pH of 7.3.

To check the pH

Check pH. Bring solution to pH 7.3 using small quantities of A or B, measured out with a pipette. Stir thoroughly. Keep in fridge until required.

NOTE: When making up buffer from older stock solutions.
Ensure any crystals formed at the bottom of the stock bottles are dissolved thoroughly before making up the buffer. Stand bottles in warm / hot water to speed the process.

Study Card Version 3.0, July 2013

Preparation of fixative

Work is conducted in a fume cupboard and wearing gloves.
Add 10mls of 25% glutaraldehyde to 50mls 0.2M sodium phosphate buffer and dilute with 40ml distilled water and mix well.
Label with contents, date made up and expiry date (one month) and "Harmful" warning label
Keep "*PGP*" well stoppered in fridge.
Decant into specimen vials. Ensure specimens are immersed in sufficient fixative – the volume of fixative should be at least 10 to 20 times the volume of the specimens. Ensure all lids are tightly closed.

Cleaning up

Rinse glassware in fume cupboard before transferring to lab sink for further washing. Wash using detergent and rinse well, giving final rinse in distilled water.
Label all vials with the appropriate 'HAZARD' label plus one which states the concentration of glutaraldehyde and 'EM FIXATIVE'.
Discard all unused fixative after 1 month and replace with fresh.
Always discard down the sink in the fume cupboard with extraction on and plenty of running water.

For any further advice on EM preparation and processing contact:
Dr Liz Curtis
Clinical; Scientist
Electron Microscopy Unit
Queen Elizabeth Hospital Birmingham
Birmingham
[redacted]
Tel: [redacted]

Addresses for Dispatch of EM Samples
EM samples in glutaraldehyde to be sent to:
Dr Desley Neil
DEVELOP-UK study
Electron Microscopy Unit
Department of Cellular Pathology
Level -1 Queen Elizabeth Hospital Birmingham
Edgbaston
Birmingham
B15 2WB

Study Card Version 3.0, July 2013

EVLP NUMBER	
DATE (dd/mm/yyyy)	☐☐/☐☐/☐☐☐☐
TIME (hh:mm)	☐☐:☐☐
TRANSPLANTED	☐ **YES** ☐ **NO**
Donor Consent for Research	☐ **YES** ☐ **NO** ☐ **UNKNOWN**

Study Card Version 3.0, July 2013

		BAL 1 Pre-EVLP	BAL 2 Post-EVLP
The duration of perfusion before BAL 2 is taken			
The lobe and segment the BAL is performed in			
The volume of saline administered			
The volume of BAL retrieved			
Beginning of sample processing: Date (dd/mm/yyyy) Time (hh:min)		/ /	
Volume of BAL after filtration (ml)	**A**		
Volume D-PBS added to cell pellet (ml)	**B**		
Total Cell Count	**C**		
Total Cell Count / 4 x 10^4	**D**		
Cell Count x Volume D-PBS	**D x B = E**		
Cell Count / Volume of BAL	**E / A**		
Number of 1 ml supernatants (max 12)			
Number of Cell pellets for RNA			
Number of Cytospins produced			

Study Card Version 3.0, July 2013

Cell Differential				
	Pre Number of Cells	**%**	**Post Number of cells**	**%**
Macrophages				
Neutrophils				
Lymphocytes				
Eosinophils				
Total				
Ciliated Epithelia				
Metaplastic Epithelia				
Total				

Study Card Version 3.0, July 2013

Perfusate Samples										
	P0	**P1**	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	**P8**	**Px**
Number of Perfusate samples (stored at -80)										

Donor Lung Biopsy			
List numbers of lung tissue specimens stored			
	Formalin	**EM**	**Snap Frozen**
Biopsy 1 prior to EVLP			
Biopsy 2 post EVLP			
List specimens transferred and centre to which moved			
EM transfer date (dd/mm/yyyy)	/ /		
Frozen transfer date (dd/mm/yyyy)	/ /		
Paraffin transfer date (dd/mm/yyyy)	/ /		
Responsibility			

Study Card Version 3.0, July 2013

Method for the preparation of a standard 2.5% glutaraldehyde fixative in 0.1M sodium phosphate buffer - for electron microscopy.

Contains a **Hazardous** chemical, read COSHH data sheet before preparing fixative for the first time.

1. Materials and Equipment

1.1. Suppliers:

Glutaraldehyde EM grade (25%) Catalogue no. R1011

Agar Scientific Ltd
Unit 7, M11 Business Link, Parsonage Lane,
Stansted, Essex, CM24 8GF
Tel: [redacted]
Email: [redacted]

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di-Sodium hydrogen orthophosphate
Sodium di-hydrogen orthophosphate

VWR International Ltd.

Hunter Boulevard

Magna Park

Lutterworth

LE17 4XN

Customer service centre: [redacted]

---

balance

500ml measuring cylinder

100ml measuring cylinder

gloves

clean 500ml bottles with well fitting stoppers

Study Card Version 3.0, July 2013

Procedure

2.1 Preparation of 0.2m sodium phosphate buffer

1.1.1. To make up stock solutions

Acidic solution (A): 31.2g/l sodium di-hydrogen orthophosphate is an 0.2M solution

Weigh out 15.6g of A; put powder in 500ml measuring cylinder, half fill with distilled water, shake until dissolved and top up to 500ml. Transfer to a clean 500ml bottle and stopper tightly. Label with 3 months expiry date

Basic solution (B): 28.4g/l di-Sodium hydrogen orthophosphate is an 0.2M solution

Weigh out 14.2g of B. Prepare and label 'Solution B' as above.

1.1.2. To make up 0.2m buffer

To make 100ml of 0.2m sodium phosphate buffer measure out 23mls of solution A and 77mls of solution B in to a beaker. Mix thoroughly. This should give a pH of 7.3.

1.1.3. To check the pH

Check pH. Bring solution to pH 7.3 using small quantities of A or B, measured out with a pipette. Stir thoroughly.

Keep in fridge until required.

1.1.4. NOTE: When making up buffer from older stock solutions.

Ensure any crystals formed at the bottom of the stock bottles are dissolved thoroughly before making up the buffer. Stand bottles in warm / hot water to speed the process.

1.2. Preparation of fixative

Work is conducted in fume cupboard

Wear gloves

Add 10mls of 25% glutaraldehyde to 50mls 0.2M sodium phosphate buffer and dilute with

40ml distilled water.

Mix well.

Label with contents, date made up and expiry date (one month) and "Harmful"

Keep "*PGP*" well stoppered in fridge.

Decant into specimen vials. Ensure specimens are immersed in sufficient fixative – the volume of fixative should be at least 10 to 20 times the volume of the specimens. Ensure all lids are tightly closed.

2. Cleaning up

Rinse glassware in fume cupboard before transferring to lab sink for further washing. Wash using detergent and rinse well, giving final rinse in distilled water.

Study Card Version 3.0, July 2013

Label all vials with the appropriate 'HAZARD' label plus one which states the concentration of glutaraldehyde and 'EM FIXATIVE'.

Discard all unused fixative after 1 month and replace with fresh.

Always discard down the sink in the fume cupboard with extraction on and plenty of running water.

Dr Liz Curtis
Clinical; Scientist

EM Unit
Level -1
Cellular Pathology Department
Queen Elizabeth Hospital Birmingham
Mindelsohn Way
Edgbaston
Birmingham B15 2WB

[redacted]

Any other SOPs?

There are: Donor offer pathway document
Sample collection data sheet
ex vivo Vivoline machine protocol
Guide to Primary Graft Dysfunction

Appendix 3 Expression of interest form version 3.0, 20 February 2013

To be printed on the local trust headed paper

Date:

Patient's name and Address:

Dear.....

RE: DEVELOP-UK
A Study of Donor Ex-vivo Lung Perfusion
in United Kingdom Lung Transplantation

I am contacting you because you are on the active waiting list for a lung transplantation and would like to invite you to consider taking part in the **DEVELOP-UK** study. This letter will be followed by a telephone call within one week by one of the research team to answer any questions you may have after reading the detailed patient information sheet and to ask about your willingness to take part.

The **DEVELOP-UK** study is funded by the Department of Health and the UK Cystic Fibrosis Trust and is being performed in all 5 adult lung transplant centres in the UK. The study aims to examine how effective a new technique called Ex-Vivo Lung Perfusion (known as EVLP) is at assessing and improving the function of donor lungs before transplant.

The shortage of donor lungs is made worse because many possible donor lungs are found to be unusable for transplant because their function is not good enough. EVLP is a new technique in which unusable donor lungs which have poor function or in which the function is uncertain, can be carefully assessed and often improved to allow their safe use in lung transplantation.

However EVLP is not yet part of standard practice and the **DEVELOP-UK** study will test whether this new technology is effective at safely increasing the number of lung transplants performed in the UK and help decide if it should become standard practice. The study will observe how the condition of patients who have received EVLP assessed and improved donor lung(s) compares in the first 12 months after their transplant to patients that have received standard donor lung(s).

Agreeing to take part in the study means you may be offered the chance of receiving EVLP assessed and improved donor lung(s) if they are found to be a good match for you. This will certainly increase the number of possible donor lungs available to you but may not necessarily mean you will get your transplant performed more quickly. You will not need any extra visits to the hospital for the study as all results will be collected at the time you attend for your usual hospital visits after transplant.

The study also involves completing a short **Quality of Life Questionnaire** before your transplant surgery, and at 3 and 6 months after receiving a lung transplant.

Some but not all patients taking part in the study will be invited to take part in a **detailed interview** with a researcher to identify, describe, and understand views of

EVLP before and after lung transplantation. Taking part in the interview is optional and does not affect your opportunity to participate in the **DEVELOP-UK** study.

In order to provide you with more information about the study, I have enclosed a detailed patient information leaflet. Please read the leaflet and feel free to discuss the study with your family and/or friends.

After you have had a telephone call from the research team we will ask you to complete the **Expression of Interest Form** that accompanies this letter. It will ask you to declare whether or not you are interested in taking part in the **DEVELOP-UK** study.

When your completed **Expression of Interest Form** is received your response will be recorded on the transplant waiting list. If you declared an interest in participating in **DEVELOP-UK** you will be able to sign the Informed Consent Form when you attend a hospital appointment at the transplant centre or when called into the transplant centre for a potential lung transplant. When you are called for a potential lung transplant you will be told whether you are to receive a standard donor lung(s) or an EVLP assessed and improved donor lung(s). If you have been told that you are to receive an EVLP assessed and improved donor lung (s), then you will be asked whether you wish to continue with the study and confirm your consent.

Thank you for taking the time to read the information sheet regarding this research study. Please tick the appropriate boxes on the form, and return it in the enclosed reply-paid envelope. If you do not wish to take part you don't have to return the form, but it would be helpful for us if you could.

If you have any questions please do not hesitate to contact me:
(Name and signature of local PI and contact phone number)

DEVELOP-UK Expression of Interest Form

Name (capitals)	
Date	
Signature	
Telephone number and/or email address	
Best time to contact me	

Please initial all boxes that apply

Yes, I am interested in taking part in the DEVELOP-UK study.
I understand that I can withdraw my interest at any time and that my
current and future care will continue exactly as before.

☐ **Initial in box**

No, I am not interested in taking part in this research study.
I understand that my current and future care will continue exactly as
Before but I understand I can change my mind in the future and contact the transplant team to express my interest.

☐ **Initial in box**

If you answered YES to an interest in taking part in the DEVELOP-UK study, please complete the question below about the Interview study:

Yes, I am willing to be contacted about a detailed interview with a researcher. I understand that I can withdraw my interest in this interview at any time and that my participation in DEVELOP-UK study will not be affected.

☐ **Initial in box**

No, I do not wish to be contacted about a detailed interview with a researcher. I understand that my participation in the DEVELOP-UK study will not be affected.

☐ **Initial in box**

Please return the completed Expression of Interest Form in the enclosed prepaid envelope to:
Address of the relevant transplant centre

Appendix 4 Informed consent forms

Donor **(in PDF form in eTMF)**

Consent Form Main Study Participant v 5.0, 24 May 2013

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 24 May 2013 (version 5.0) 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

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

Consent Form Interview Study Participant v 1.0, 1 November 2011

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.

Consent Form Interview Study Nominated Carer v 1.0, 1 November 2011

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

Nominated relative or Carer 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 have received enough information about the study and I understand what the study involves. ☐
3. I understand that this part of the study is purely optional. I understand I will not be contacted again with regards to the interview study if the person I care for is not to be involved. ☐
4. I understand that 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 Relative or Carer	Date	Signature
_____	_____	_____
Name of person taking consent (if different from PI)	Date	Signature
_____	_____	_____
Principal Investigator	Date	Signature

When completed: one copy to relative/carer; one copy for hospital record; original copy to Site Investigator File.

Consent Form Study Participant after standard lung transplant v 1.0, 24 May 2013

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

(After Standard Lung Transplant)

Please initial box

1. I confirm that I have read and understand the Participant Information Sheet dated 24 May 2013 (version 5.0) 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. 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. ☐
5. 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. ☐
6. I agree to my GP being informed of my participation in the study. ☐

7. 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

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

Consent to continue Form Main Study Participant v 5.0, 24 May 2013

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 to Continue Form
(FOR EVLP TRANSPLANTS ONLY)

Please initial box

1. I confirm that I have read and understand the Participant Information Sheet dated 24 May 2013 (version 5.0) 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

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

Appendix 5 Hospital staff resource use survey

Qualtrics survey

In September 2014, a survey was conducted in order to determine the hospital resource use and staff time after lung transplant. In this survey, most of the hospital staff who took part in the DEVELOP-UK study were involved. The survey was conducted using the online Qualtrics software.

Questions

The questions asked to each member of the hospital staff are presented below.

Consultant surgeon/surgical fellow/consultant physician

Question 1

On the day/night of lung transplantation how much time do you spend preparing for the surgery (i.e. on the telephone or in discussion with other team members)?

Question 2

How long do you spend in theatre undertaking the lung transplant procedure?

Question 3

Post operation, how long is it before you leave the hospital/are ready to see another patient?

Question 4

How much time do you spend in ITU on a daily basis with a straightforward, uncomplicated lung transplant patient who requires single organ support or remains in single organ failure?

Question 5

How much time do you spend in ITU on a daily basis with a lung transplant patient experiencing more severe complications with multiorgan failure?

Question 6

In a more specific example, how much time do you spend each day with lung transplant patients on ECMO (extracorporeal membrane oxygenation)?

Question 7

How much time do you spend on a daily basis with a lung transplant patient in level 1 ward-based care?

Additional comments

Any additional comments you have regarding the time you input into the care of lung transplant patients would be greatly appreciated.

Consultant anaesthetist/anaesthetic fellow

Question 1

On the day/night of lung transplantation how much time do you spend preparing the patient for anaesthesia?

Question 2

How much time do you spend preparing for the surgery (i.e. discussing with colleagues and transplant co-ordinators)?

Question 3
How much time do you spend in theatre supervising the patient during anaesthesia?

Question 4
How much time do you spend bringing the patient back to ITU to stabilise them?

Question 5
How much time do you spend in ITU on a daily basis with a straightforward, uncomplicated lung transplant patient who requires single organ support or remains in single organ failure?

Question 6
How much time do you spend in ITU on a daily basis with a lung transplant patient experiencing more severe complications with multiorgan failure?

Question 7
In a more specific example, how much time do you spend each day with lung transplant patients on ECMO (extracorporeal membrane oxygenation)?

Question 9
How much time do you spend on a daily basis with a lung transplant patient in level 1 ward-based care?

Additional comments
Any additional comments you have regarding the time you input into the care of lung transplant patients would be greatly appreciated.

Transplant co-ordinator

Question 1
How long do you spend in hospital once organs have arrived?

Question 2
How long do you spend in theatre on day/night of transplant?

Question 3
Do you spend time with the relatives of the patient post transplant?

Question 4
How long do you spend with the relatives of the patient post transplant (e.g. comforting them, helping to sort out accommodation for the night if needed)?

Additional comments
Any additional comments you have regarding the time you input into the care of lung transplant patients would be greatly appreciated.

Responses

Table 48 shows the number of responses from the hospital staff resource use survey.

Table 49 shows the number of complete responses per each member of the staff.

TABLE 48 Responses to survey

Response details	First draft	New survey	Total
Total number of responses	24	89	113
Completed responses	2	41	43
Blank responses: initial question not displayed	0	6	6
Blank responses: initial question not answered	2	9	11
Job role only: no questions displayed	6	8	14
Job role only: no questions answered	8	13	21
Job role only: mix of questions not displayed or answered	6	12	18

TABLE 49 Complete responses to survey per each member of staff

Member of staff	Completed responses
Consultant surgeon	7
Surgical fellow	4
Consultant physician	8
Physician fellow	0
Consultant anaesthetist	8
Anaesthetic fellow	3
Transplant co-ordinator	13
Total	43

Appendix 6 Unit costs of resources and interventions

TABLE 50 Unit costs of resources and interventions: detailed

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Donor's hospital					
Fixed costs					
Initial assessment					
ABG	Test	Donor	4.37	4.37	NuTH's costing tool[99]
Bronchoscopy	Procedure	Donor	340.00	340.00	*Reference Costs 2013/2014*[49]
Chest X-ray (radiography)	Test	Donor	24.97	24.97	NuTH's costing tool[99]
ECG	Test	Donor	20.81	20.81	NuTH's costing tool[99]
FBC	Test	Donor	4.94	4.94	NuTH's costing tool[99]
Drugs					
Methylprednisolone (as sodium succinate)	500-mg vial	Donor	9.60	9.60	BNF 2014[50]
Methylprednisolone (as sodium succinate)	1-g vial	Donor	17.30	17.30	BNF 2014[50]
Methylprednisolone (as sodium succinate)	2-g vial	Donor	32.66	32.66	BNF 2014[50]
Lung retrieval					
Fixed costs					
Equipment					
DCD donor					
Bronchoscope	Instrument	Donor	8.18	8.18	EAC
Pink spray 0.5% chlorhexidine	Spray	Donor	3.69	3.69	Medical supplies
2 l of 0.9% sodium chloride solution	1-l solution	Donor	0.97	0.97	NHSBSA's *Amendments to the Drug Tariff*[100]
Strapple tape	Roll	Donor	2.00	2.00	Medical supplies
DBD donor					
Blue 23-gauge 25-mm (1-inch) needles	1-inch needle	Donor	0.05	0.05	Medical supplies
Bronchoscope	Instrument	Donor	8.18	8.18	EAC
1-l cardioplegia bag (green PLEGIVEX, Ivex Pharmaceuticals Ltd, Larne, UK)	1-l bag	Donor	35.92	35.92	Medical supplies
Green vacutainers	Vacutainer	Donor	0.13	0.13	Medical supplies
i-STAT portable clinical analyser	Device	Donor	3.13	3.13	EAC

continued

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
i-STAT cartridges	Cartridge	Donor	8.00	8.00	Paul Henderson, NuTH, September 2014, personal communication
Pink spray 0.5% chlorhexidine	Spray	Donor	3.69	3.69	Medical supplies
1-l pressure infusion bag	1-l bag	Donor	49.99	49.99	Medical supplies
Red vacutainers	Vacutainer	Donor	0.12	0.12	Medical supplies
10 ml of 8.4% sodium bicarbonate	10-ml ampoule	Donor	11.03	11.03	BNF 2014[50]
2 l of 0.9% sodium chloride solution	1-l solution	Donor	0.97	0.97	NHSBSA's *Amendments to the Drug Tariff*[100]
Spleen pots	Pot	Donor	0.41	0.41	Medical supplies
Strapple tape	Roll	Donor	2.00	2.00	Medical supplies
1-ml syringes	1-ml syringe	Donor	0.08	0.08	Medical supplies
Staff time					
Scout team					
Retrieval surgeon (fellow)	Hour	Donor	56.41	56.41	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Scrub nurse (band 5)	Hour	Donor	20.31	20.31	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Retrieval team					
Perfusionist (band 7)	Hour	Donor	28.09	28.09	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Retrieval surgeon (fellow)	Hour	Donor	56.41	56.41	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Scrub nurse (band 5)	Hour	Donor	20.31	20.31	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Tests					
Chest X-ray (radiography)	Test	Donor	24.97	24.97	NuTH's costing tool[99]
Perfusion (dosage)					
2.8 l of PERFADEX solution	2.8-l solution	Donor	376.00	376.00	XVIVO[101]
1 l of PERFADEX solution	1-l solution	Donor	134.24	134.24	XVIVO[101]
$CaCl_2$ 1 mmol/ml (1.7 ml/2.8 l PERFADEX and 0.6 ml/1 l PERFADEX)	10-ml ampoule	Donor	14.94	14.94	BNF 2014[50]
FLOLAN 0.5-mg vial (7 ml/2.8 l PERFADEX)	0.5-mg vial	Donor	22.22	22.22	BNF 2014[50]
FLOLAN 0.5-mg vial (2.5 ml/1 l PERFADEX)	0.5-mg vial	Donor	22.22	22.22	BNF 2014[50]

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Heparin sodium 5000 units/5 ml (15,000 units/2.8 l PERFADEX)	5-ml ampoule	Donor	7.58	7.58	BNF 2014[50]
Heparin sodium 5000 units/5 ml (5000 units/1 l PERFADEX)	5-ml ampoule	Donor	7.58	7.58	BNF 2014[50]
THAM 1-ml ampoule (7 ml/2.8 l PERFADEX)	1-ml ampoule	Donor	1.07	1.07	BNF 2014[50]
THAM 1-ml ampoule (2.5 ml/1 l PERFADEX)	1-ml ampoule	Donor	1.07	1.07	BNF 2014[50]
Variable costs					
Travelling					
Scout team					
Road	Transport type	Donor	225.00	225.00	Brian Leadbitter, NuTH, June 2015, personal communication
Retrieval team					
Road	Transport type	Donor	297.00	297.00	Brian Leadbitter, NuTH, June 2015, personal communication
Road and air	Transport type	Donor	9791.00	9791.00	Brian Leadbitter, NuTH, June 2015, personal communication
Organ (lung)					
Road	Transport type	Donor	392.00	392.00	Brian Leadbitter, NuTH, June 2015, personal communication
Road and air	Transport type	Donor	7527.00	7527.00	Brian Leadbitter, NuTH, June 2015, personal communication
Transplant preparation *Fixed costs*					
Contacting potential recipients					
Transplant co-ordinator	Hour	Recipient	30.41	30.41	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Meeting potential recipients					
Transplant co-ordinator	Hour	Recipient	30.41	30.41	PSSRU's *Unit Costs of Health and Social Care 2014*[51]

continued

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Tissue typing					
Tissue typing test	Test	Recipient	59.87	59.87	ISD Scotland's *About ISD*[102]
Tests					
ABG	Test	Recipient	4.37	4.37	NuTH's costing tool[99]
Chest X-ray (radiography)	Test	Recipient	24.97	24.97	NuTH's costing tool[99]
ECG	Test	Recipient	20.81	20.81	NuTH's costing tool[99]
FBC	Test	Recipient	4.94	4.94	NuTH's costing tool[99]
Ward time					
Transplant centre ward	Bed-day	Recipient	265.00	265.00	*Reference Costs 2013/2014*[49]
Drugs					
Azathioprine, 50 mg	56-tablet pack	Recipient	3.48	3.48	BNF 2014[50]
Variable costs					
Transfer to ward					
Air	Transport type	Recipient	Missing	Missing	Missing
Road	Transport type	Recipient	Missing	Missing	Missing
EVLP procedure *Fixed costs*					
Staff time					
Anaesthetic registrar	Hour	EVLP recipient	–	22.84	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Consultant surgeon	Hour	EVLP recipient	–	60.11	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Perfusionist (band 7)	Hour	EVLP recipient	–	28.09	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Scrub nurse/ODA (band 5)	Hour	EVLP recipient	–	20.31	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Surgical fellow	Hour	EVLP recipient	–	56.41	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Equipment					
Bronchoscope	Instrument	EVLP recipient	–	8.18	EAC
DeBakey tissue forceps	Forceps	EVLP recipient	–	0.08	EAC
McIndoe scissors	Scissors	EVLP recipient	–	1.65	Medical supplies

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Nebuliser circuit	Item	EVLP recipient	–	1.32	Paul Henderson, NuTH, September 2014, personal communication
4–0 Prolene (No. 8935) suture pack (Ethicon Inc., Somerville, NJ, USA)	Pack	EVLP recipient	–	2.87	Anna Soderlund, Vivoline, July 2014, personal communication
10-fg suction catheter (SHODS)	Catheter	EVLP recipient	–	0.45	Medical supplies
Suction connecting tubing	Tubing	EVLP recipient	–	2.36	Paul Henderson, NuTH, September 2014, personal communication
Consumables					
Nylon surgical tape	Roll	EVLP recipient	–	1.56	Medical supplies
Gas (2000 l of N_2/CO_2)	Cylinder	EVLP recipient	–	400.00	Anna Soderlund, Vivoline, July 2014, personal communication
PERFADEX solution	1-l solution	EVLP recipient	–	134.24	XVIVO[101]
Packed red blood cells	274-ml bag	EVLP recipient	–	120.00	Paul Henderson, NuTH, September 2014, personal communication/ Yvonne Scott, NuTH, July 2015, personal communication
Syringes for blood gases	Syringe	EVLP recipient	–	0.36	Medical supplies
Syringes (other)	Syringe	EVLP recipient	–	0.08	Medical supplies
Vivoline disposable lung set	Set	EVLP recipient	–	6962.87	Anna Soderlund, Vivoline, July 2014, personal communication
Miscellaneous equipment					
Blood gases samples	Sample	EVLP recipient	–	1.77	Paul Henderson, NuTH, September 2014, personal communication
Vivoline system	System	EVLP recipient	–	39.40	EAC
Theatre usage					
Operating theatre	Hour	EVLP recipient	–	587.66	ISD Scotland's *About ISD*[102]

continued

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Drugs					
2 l of Steen Solution	500-ml solution	EVLP recipient	–	528.36	XVIVO[101]
Heparin sodium, 1000 units/ml	1-ml ampoule	EVLP recipient	–	1.49	BNF 2014[50]
Heparin sodium, 5000 units/ml	1-ml ampoule	EVLP recipient	–	7.58	BNF 2014[50]
Insulin human [ACTRAPID® HM (Novo Nordisk, Bagsværd, Denmark)], 100 IU/ml	10-ml vial	EVLP recipient	–	7.48	BNF 2014[50]
Methylprednisolone (as sodium succinate)	500-mg vial	EVLP recipient	–	9.60	BNF 2014[50]
Methylprednisolone (as sodium succinate)	1-g vial	EVLP recipient	–	17.30	BNF 2014[50]
Methylprednisolone (as sodium succinate)	2-g vial	EVLP recipient	–	32.66	BNF 2014[50]
THAM, 30 mg/ml (3.0 mmol/ml)	1-ml ampoule	EVLP recipient	–	1.07	BNF 2014[50]
Antibiotics					
Meropenem (as trihydrate)	500-mg vial	EVLP recipient	–	8.00	BNF 2014[50]
Moxifloxacin (as hydrochloride), 1.6 mg/ml	250-ml solution for infusion bottle (400 mg)	EVLP recipient	–	12.43	BNF 2014[50]
Antifungal					
Amphotericin B	50-mg vial	EVLP recipient	–	3.88	BNF 2014[50]
Lung transplant *Fixed costs*					
Anaesthetic preparation					
Anaesthetic room	Hour	Recipient	587.66	587.66	ISD Scotland's *About ISD*[102]
Anaesthetic nurse (band 5)	Hour	Recipient	20.31	20.31	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Consultant anaesthetist	Hour	Recipient	59.37	59.37	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Staff time					
Single lung surgery					
Anaesthetic fellow	Hour	Recipient	56.41	56.41	PSSRU's *Unit Costs of Health and Social Care 2014*[51]

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Anaesthetic nurse (band 5)	Hour	Recipient	20.31	20.31	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Consultant anaesthetist	Hour	Recipient	59.37	59.37	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Consultant surgeon	Hour	Recipient	60.11	60.11	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Perfusionist (band 7)	Hour	Recipient	28.09	28.09	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Scrub nurse (band 7)	Hour	Recipient	30.34	30.34	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Scrub nurse (band 5)	Hour	Recipient	20.31	20.31	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Surgical fellow	Hour	Recipient	56.41	56.41	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Double lung surgery					
Anaesthetic fellow	Hour	Recipient	56.41	56.41	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Anaesthetic nurse (band 5)	Hour	Recipient	20.31	20.31	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Consultant anaesthetist	Hour	Recipient	59.37	59.37	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Consultant surgeon	Hour	Recipient	60.11	60.11	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Perfusionist (band 7)	Hour	Recipient	28.09	28.09	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Scrub nurse (band 7)	Hour	Recipient	30.34	30.34	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Scrub nurse (band 5)	Hour	Recipient	20.31	20.31	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Surgical fellow	Hour	Recipient	56.41	56.41	PSSRU's *Unit Costs of Health and Social Care 2014*[51]

continued

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Theatre usage					
Single lung surgery					
Operating theatre	Hour	Recipient	587.66	587.66	ISD Scotland's *About ISD*[102]
Double lung surgery					
Operating theatre	Hour	Recipient	587.66	587.66	ISD Scotland's *About ISD*[102]
Equipment/consumables					
Usual surgical set	Set	Recipient	Missing	Missing	Missing
Post-operative care *Fixed costs*					
Staff time in ITU/HDU					
Anaesthetic fellow	Hour	Recipient	56.41	56.41	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Consultant anaesthetist	Hour	Recipient	59.37	59.37	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Consultant physician	Hour	Recipient	59.37	59.37	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Consultant surgeon	Hour	Recipient	60.11	60.11	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Surgical fellow	Hour	Recipient	56.41	56.41	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Staff time in hospital					
Consultant physician	Hour	Recipient	59.37	59.37	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Surgical fellow	Hour	Recipient	56.41	56.41	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Transplant specialist registrar	Hour	Recipient	40.00	40.00	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Tests					
ABG	Test	Recipient	4.37	4.37	NuTH's costing tool[99]
Chest X-ray (radiography)	Test	Recipient	24.97	24.97	NuTH's costing tool[99]
FBC	Test	Recipient	4.94	4.94	NuTH's costing tool[99]
Pulmonary/lung function test	Test	Recipient	169.00	169.00	*Reference Costs 2013/2014*[49]

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Variable costs					
***Ward usage* (if needed)**					
HDU care	Bed-day	Recipient	852.00	852.00	*Reference Costs 2013/2014*[49]
ITU care	Bed-day	Recipient	852.00	852.00	*Reference Costs 2013/2014*[49]
ITU/HDU readmission	Bed-day	Recipient	852.00	852.00	*Reference Costs 2013/2014*[49]
Level 1 ward care (hospital stay)	Bed-day	Recipient	265.00	265.00	*Reference Costs 2013/2014*[49]
***Procedures* (if needed)**					
Bronchoscopy	Procedure	Recipient	340.00	340.00	*Reference Costs 2013/2014*[49]
Tracheostomy	Procedure	Recipient	135.00	135.00	*Reference Costs 2013/2014*[49]
***Equipment* (if needed)**					
ECMO	Machine	Recipient	34,000.00	34,000.00	Tanveer Butt, NuTH, June 2015, personal communication
iLA membrane ventilator	Device	Recipient	4.28	4.28	EAC
***Consumables* (if needed)**					
2 l colloid (plasma and plasma substitutes)	500 ml	Recipient	8.00	8.00	BNF 2014[50]
1 l crystalloid (fluids containing electrolytes)	500 ml	Recipient	8.00	8.00	BNF 2014[50]
Fresh-frozen plasma	271-ml bag	Recipient	28.46	28.46	NHSBT
Packed red blood cells	274-ml bag	Recipient	120.00	120.00	Paul Henderson, NuTH, September 2014, personal communication/ Yvonne Scott, NuTH, July 2015, personal communication
Platelets	250-ml bag	Recipient	196.96	196.96	NHSBT
***Inotropes* (if needed)**					
Adrenaline (base), 1 mg/10 ml (1 in 10,000)	10-ml pre-filled disposable injection	Recipient	6.99	6.99	BNF 2014[50]
Dobutamine (as hydrochloride), 12.5 mg/ml	20-ml ampoule	Recipient	5.20	5.20	BNF 2014[50]
Glyceryl trinitrate, 1 mg/ml	50-ml vial	Recipient	15.90	15.90	BNF 2014[50]
Milrinone, 1 mg/ml	10-ml ampoule	Recipient	19.91	19.91	BNF 2014[50]
Noradrenaline (as acid tartrate), 1 mg/ml	4-ml ampoule	Recipient	4.40	4.40	BNF 2014[50]

continued

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Pitressin (argipressin – synthetic vasopressin), 20 units/ml	1-ml ampoule	Recipient	22.50	22.50	BNF 2014[50]
Other					
Dopamine hydrochloride, 40 mg/ml	5-ml ampoule	Recipient	3.88	3.88	BNF 2014[50]
Enoximone, 5 mg/ml	20-ml ampoule	Recipient	15.02	15.02	BNF 2014[50]
Isoprenaline	–	Recipient	5.20	5.20	–
Metaraminol	–	Recipient	4.40	4.40	–
***Post-implantation haemodynamic support* (if needed)**					
Adrenaline (base), 1 mg/10 ml (1 in 10,000)	10-ml pre-filled disposable injection	Recipient	6.99	6.99	BNF 2014[50]
Dobutamine (as hydrochloride), 12.5 mg/ml	20-ml ampoule	Recipient	5.20	5.20	BNF 2014[50]
Glyceryl trinitrate, 1 mg/ml	50-ml vial	Recipient	15.90	15.90	BNF 2014[50]
Milrinone, 1 mg/ml	10-ml ampoule	Recipient	19.91	19.91	BNF 2014[50]
Noradrenaline (as acid tartrate), 1 mg/ml	4-ml ampoule	Recipient	4.40	4.40	BNF 2014[50]
Pitressin (argipressin – synthetic vasopressin), 20 units/ml	1-ml ampoule	Recipient	22.50	22.50	BNF 2014[50]
***Complications* (if reported)**					
Cerebrovascular accident	Treatment	Recipient	840.65	840.65	*Reference Costs 2013/2014*[49]
Haemofiltration	Procedure	Recipient	139.00	139.00	*Reference Costs 2013/2014*[49]
Haemodialysis	Procedure (days)	Recipient	139.00	139.00	*Reference Costs 2013/2014*[49]
Re-exploration	Procedure	Recipient	4580.36	4580.36	*Reference Costs 2013/2014*[49]
***Airway complications* (if reported)**					
Balloon dilatation	Procedure	Recipient	4580.36	4580.36	*Reference Costs 2013/2014*[49]
Cryotherapy	Procedure	Recipient	4580.36	4580.36	*Reference Costs 2013/2014*[49]
Diathermy	Procedure	Recipient	4580.36	4580.36	*Reference Costs 2013/2014*[49]
Stenting	Procedure	Recipient	4580.36	4580.36	*Reference Costs 2013/2014*[49]
Surgical intervention	Procedure	Recipient	4580.36	4580.36	*Reference Costs 2013/2014*[49]

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
ITU rejection episodes **(if reported)**					
Ward usage					
HDU care	Bed-day	Recipient	852.00	852.00	*Reference Costs 2013/2014*[49]
ITU care	Bed-day	Recipient	852.00	852.00	*Reference Costs 2013/2014*[49]
Procedures					
Clinical diagnosis/biopsy	Procedure	Recipient	851.00	851.00	*Reference Costs 2013/2014*[49]
Treatment					
Cefuroxime (as sodium)	750-mg vial	Recipient	2.52	2.52	BNF 2014[50]
Methylprednisolone (as sodium succinate)	1-g vial	Recipient	17.30	17.30	BNF 2014[50]
Piperacillin (as sodium), 2 g; and tazobactam (as sodium), 250 mg (Tazocin®, Pfizer Ltd, New York City, NY, USA)	2.25-g vial	Recipient	7.65	7.65	BNF 2014[50]
Changes in maintenance therapy					
Methylprednisolone, 100 mg	20-tablet pack	Recipient	48.32	48.32	BNF 2014[50]
Tacrolimus, 5 mg/ml	1-ml ampoule	Recipient	58.45	58.45	BNF 2014[50]
Ward rejection episodes **(if reported)**					
Procedures					
Clinical diagnosis/biopsy	Procedure	Recipient	851.00	851.00	*Reference Costs 2013/2014*[49]
Treatment					
Methylprednisolone (as sodium succinate)	500-mg vial	Recipient	9.60	9.60	BNF 2014[50]
Methylprednisolone (as sodium succinate)	1-g vial	Recipient	17.30	17.30	BNF 2014[50]
Methylprednisolone, 100 mg	20-tablet pack	Recipient	48.32	48.32	BNF 2014[50]
Prednisolone acetate, 25 mg/ml	1-ml ampoule	Recipient	6.87	6.87	BNF 2014[50]
Prednisolone, 25 mg	56-tablet pack	Recipient	50.00	50.00	BNF 2014[50]
Sulfamethoxazole, 400 mg; and trimethoprim, 80 mg (co-trimoxazole) 480 mg	28-tablet pack	Recipient	3.34	3.34	BNF 2014[50]
Tacrolimus, 5 mg/ml	1-ml ampoule	Recipient	58.45	58.45	BNF 2014[50]

continued

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
***Infection episodes* (if reported)**					
Treatment					
Aciclovir (as sodium), 25 mg/ml	20-ml vial (500 mg)	Recipient	19.61	19.61	BNF 2014[50]
Adefovir dipivoxil, 10 mg	30-tablet pack	Recipient	252.22	252.22	BNF 2014[50]
Amikacin (as sulfate), 250 mg/ml	2-ml vial	Recipient	9.64	9.64	BNF 2014[50]
Amoxicillin (as trihydrate), 500 mg	21-capsule pack	Recipient	1.62	1.62	BNF 2014[50]
Amoxicillin (as trihydrate), 500 mg; and clavulanic acid (as potassium), 125 mg (co-amoxiclav)	21-tablet pack	Recipient	4.23	4.23	BNF 2014[50]
Amphotericin B liposomal (AmBisome®)	50-mg vial	Recipient	82.19	82.19	BNF 2014[50]
Amphotericin B (as sodium deoxycholate complex)	50-mg vial	Recipient	3.88	3.88	BNF 2014[50]
Anidulafungin	100-mg vial	Recipient	299.99	299.99	BNF 2014[50]
Azithromycin (as dihydrate), 250 mg	4-capsule pack	Recipient	10.06	10.06	BNF 2014[50]
Aztreonam	1-g vial	Recipient	9.40	9.40	BNF 2014[50]
BAL	Procedure	Recipient	340.00	340.00	*Reference Costs 2013/2014*[49]
Budesonide, 100 µg; and formoterol fumarate, 6 µg [Symbicort Turbohaler® (AstraZeneca, London, UK)]	120-dose inhaler	Recipient	33.00	33.00	BNF 2014[50]
Caspofungin (as acetate)	70-mg vial	Recipient	416.78	416.78	BNF 2014[50]
Ceftazidime (as pentahydrate)	2-g vial	Recipient	17.90	17.90	BNF 2014[50]
Cefuroxime (as sodium)	750-mg vial	Recipient	2.52	2.52	BNF 2014[50]
Chloramphenicol (as sodium succinate)	1-g vial	Recipient	1.39	1.39	BNF 2014[50]
Ciprofloxacin (as lactate) 2 mg/ml	200-ml solution for infusion bottle	Recipient	19.79	19.79	BNF 2014[50]
Ciprofloxacin (as hydrochloride), 500 mg	20-tablet pack	Recipient	1.47	1.47	BNF 2014[50]
Ciprofloxacin (as hydrochloride), 3 mg/ml	5-ml 0.3% eye drops	Recipient	4.70	4.70	BNF 2014[50]
Clarithromycin	500-mg vial	Recipient	9.45	9.45	BNF 2014[50]
Clindamycin (as phosphate), 150 mg/ml	4-ml ampoule	Recipient	11.80	11.80	BNF 2014[50]
Colistimethate sodium	2-million-unit vial	Recipient	3.24	3.24	BNF 2014[50]

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Domperidone (as maleate), 10 mg	100-tablet pack	Recipient	5.83	5.83	BNF 2014[50]
Doxycycline (as hyclate), 100 mg	8-capsule pack	Recipient	1.13	1.13	BNF 2014[50]
Eradication therapy for *Helicobacter pylori*	7-day course	Recipient	4.30	4.30	BNF 2014[50]
Ertapenem (as sodium)	1-g vial	Recipient	31.65	31.65	BNF 2014[50]
Ethambutol hydrochloride, 100 mg	56-tablet pack	Recipient	11.52	11.52	BNF 2014[50]
Flucloxacillin (as sodium), 500 mg	28-capsule pack	Recipient	2.60	2.60	BNF 2014[50]
Flucloxacillin (as sodium)	1-g vial	Recipient	4.90	4.90	BNF 2014[50]
Fluconazole, 50 mg	7-capsule pack	Recipient	1.02	1.02	BNF 2014[50]
Fluconazole, 2 mg/ml	100-ml solution for infusion bottle	Recipient	27.45	27.45	BNF 2014[50]
Fluconazole, 50 mg	7-capsule pack	Recipient	1.02	1.02	BNF 2014[50]
Foscarnet sodium, 24 mg/ml	250-ml solution for infusion bottle	Recipient	119.85	119.85	BNF 2014[50]
Fosfomycin (as sodium)	2-g vial	Recipient	15.00	15.00	BNF 2014[50]
Furosemide, 10 mg/ml	5-ml ampoule	Recipient	0.32	0.32	BNF 2014[50]
Ganciclovir (as sodium)	500-mg vial	Recipient	29.77	29.77	BNF 2014[50]
Gentamicin (as sulfate), 40 mg/ml	2-ml vial	Recipient	1.40	1.40	BNF 2014[50]
Immunoglobulin	10-g vial	Recipient	401.00	401.00	BNF 2014[50]
Itraconazole, 10 mg/ml	25-ml ampoule	Recipient	79.71	79.71	BNF 2014[50]
Lamivudine, 150 mg	60-tablet pack	Recipient	121.82	121.82	BNF 2014[50]
Lesion excision	Day case	Recipient	2488.00	2488.00	*Reference Costs 2013/2014*[49]
Linezolid, 2 mg/ml	300-ml infusion bag	Recipient	44.50	44.50	BNF 2014[50]
Meropenem (as trihydrate)	1-g vial	Recipient	16.00	16.00	BNF 2014[50]
Methylprednisolone (as sodium succinate)	1-g vial	Recipient	17.30	17.30	BNF 2014[50]
Metoclopramide hydrochloride, 5 mg/ml	2-ml ampoule	Recipient	0.32	0.32	BNF 2014[50]
Metronidazole, 200 mg	21-tablet pack	Recipient	6.46	6.46	BNF 2014[50]
Micafungin (as sodium)	100-mg vial	Recipient	341.00	341.00	BNF 2014[50]
Moxifloxacin (as hydrochloride), 1.6 mg/ml	250-ml solution for infusion bottle	Recipient	39.95	39.95	BNF 2014[50]
Oseltamivir (as phosphate), 75 mg	10-capsule pack	Recipient	15.41	15.41	BNF 2014[50]

continued

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Packed red blood cells	274-ml bag	Recipient	120.00	120.00	Paul Henderson, NuTH, September 2014, personal communication/ Yvonne Scott, NuTH, July 2015, personal communication
Piperacillin (as sodium), 4 g; and tazobactam (as sodium), 500 mg (Tazocin)	4.5-g vial	Recipient	12.90	12.90	BNF 2014[50]
Posaconazole, 100 mg	96-tablet pack	Recipient	2387.85	2387.85	BNF 2014[50]
Prednisolone, 25 mg	56-tablet pack	Recipient	50.00	50.00	BNF 2014[50]
Respiratory failure (inpatient)	Treatment	Recipient	3445.00	3445.00	*Reference Costs 2013/2014*[49]
Sirolimus, 2 mg	30-tablet pack	Recipient	172.98	172.98	BNF 2014[50]
Streptokinase	250,000-unit powder vial	Recipient	13.52	13.52	BNF 2014[50]
Sulfamethoxazole, 80 mg; and trimethoprim, 16 mg [Septrin® (Aspen Pharmcare Holding Ltd, Durban, South Africa)]	5-ml ampoule	Recipient	1.78	1.78	BNF 2014[50]
Surgical intervention or VATS	Procedure	Recipient	4580.36	4580.36	*Reference Costs 2013/2014*[49]
Teicoplanin	200-mg vial	Recipient	3.93	3.93	BNF 2014[50]
Trimethoprim, 100 mg	28-tablet pack	Recipient	7.55	7.55	BNF 2014[50]
Tobramycin (as sulfate), 40 mg/ml	1-ml vial	Recipient	3.70	3.70	BNF 2014[50]
Tigecycline	50-mg vial	Recipient	32.31	32.31	BNF 2014[50]
Valaciclovir (as hydrochloride), 500 mg	42-tablet pack	Recipient	8.50	8.50	BNF 2014[50]
Valganciclovir (as hydrochloride), 450 mg	60-tablet pack	Recipient	1081.46	1081.46	BNF 2014[50]
Vancomycin (as hydrochloride)	1-g vial	Recipient	12.99	12.99	BNF 2014[50]
Voriconazole	200-mg vial	Recipient	77.14	77.14	BNF 2014[50]
Ward usage					
HDU care	Bed-day	Recipient	852.00	852.00	*Reference Costs 2013/2014*[49]
ITU care	Bed-day	Recipient	852.00	852.00	*Reference Costs 2013/2014*[49]
Outpatient care					
Fixed costs					
Outpatient reviews					
Bronchoscopy	Procedure/visit (4 visits)	Recipient	340.00	340.00	*Reference Costs 2013/2014*[49]
Chest X-ray (radiography)	Test/visit (4 visits)	Recipient	24.97	24.97	NuTH's costing tool[99]

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
FBC	Test/visit (4 visits)	Recipient	4.94	4.94	NuTH's costing tool[99]
Liver function test	Test/visit (4 visits)	Recipient	6.80	6.80	NuTH's costing tool[99]
Pulmonary/lung function test	Test/visit (4 visits)	Recipient	169.00	169.00	*Reference Costs 2013/2014*[49]
Urea and electrolytes test	Test/visit (4 visits)	Recipient	2.96	2.96	NuTH's costing tool[99]
Staff time					
Consultant physician	Hour/visit (4 visits)	Recipient	59.37	59.37	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Scrub nurse (band 5)	Hour/visit (4 visits)	Recipient	20.31	20.31	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Variable costs					
***Rejection episodes* (if reported)**					
Procedures					
Clinical diagnosis/biopsy	Procedure	Recipient	295.00	295.00	*Reference Costs 2013/2014*[49]
Ventilation–perfusion scan	Test	Recipient	203.00	203.00	*Reference Costs 2013/2014*[49]
Treatment					
Anti-thymocyte immunoglobulin (rabbit), 25 mg	25-mg vial	Recipient	158.77	158.77	BNF 2014[50]
Azathioprine, 25 mg	28-tablet pack	Recipient	3.24	3.24	BNF 2014[50]
Azathioprine, 50 mg	56-tablet pack	Recipient	3.48	3.48	BNF 2014[50]
Ciclosporin, 25 mg	30-capsule pack	Recipient	13.05	13.05	BNF 2014[50]
Ciclosporin, 50 mg	30-capsule pack	Recipient	25.50	25.50	BNF 2014[50]
Ciclosporin, 100 mg	30-capsule pack	Recipient	48.50	48.50	BNF 2014[50]
Ciclosporin [NEORAL® (Novartis International AG, Basel, Switzerland)], 10 mg	60-capsule pack	Recipient	16.68	16.68	BNF 2014[50]
Ciclosporin (NEORAL), 25 mg	30-capsule pack	Recipient	16.79	16.79	BNF 2014[50]
Ciclosporin (NEORAL), 50 mg	30-capsule pack	Recipient	32.88	32.88	BNF 2014[50]
Ciclosporin (NEORAL), 100 mg	30-capsule pack	Recipient	62.41	62.41	BNF 2014[50]
Immunoglobulin	10-g vial	Recipient	401.00	401.00	BNF 2014[50]

continued

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Meropenem (as trihydrate)	1-g vial	Recipient	16.00	16.00	BNF 2014[50]
Methylprednisolone (as sodium succinate)	125-mg vial	Recipient	4.75	4.75	BNF 2014[50]
Methylprednisolone (as sodium succinate)	500-mg vial	Recipient	9.60	9.60	BNF 2014[50]
Methylprednisolone (as sodium succinate)	1-g vial	Recipient	17.30	17.30	BNF 2014[50]
Mycophenolate mofetil, 500 mg	50-tablet pack	Recipient	10.15	10.15	BNF 2014[50]
Mycophenolate mofetil (MMF), 250 mg	100-capsule pack	Recipient	82.26	82.26	BNF 2014[50]
Prednisolone, 1 mg	28-tablet pack	Recipient	1.08	1.08	BNF 2014[50]
Prednisolone, 5 mg	28-tablet pack	Recipient	1.29	1.29	BNF 2014[50]
Prednisolone, 25 mg	56-tablet pack	Recipient	50.00	50.00	BNF 2014[50]
Rituximab, 100 mg/ml	10-ml vial	Recipient	174.63	174.63	BNF 2014[50]
Tacrolimus [Prograf® (Astellas Pharma Inc., Tokyo, Japan)], 500 µg	50-capsule pack	Recipient	61.88	61.88	BNF 2014[50]
Tacrolimus (Prograf), 1 mg	50-capsule pack	Recipient	80.28	80.28	BNF 2014[50]
Tacrolimus (Prograf), 1 mg	100-capsule pack	Recipient	160.54	160.54	BNF 2014[50]
Tacrolimus (Prograf), 5 mg	50-capsule pack	Recipient	296.58	296.58	BNF 2014[50]
Valganciclovir (as hydrochloride), 450 mg	60-tablet pack	Recipient	1081.46	1081.46	BNF 2014[50]
Ward usage					
HDU care	Bed-day	Recipient	852.00	852.00	*Reference Costs 2013/2014*[49]
ITU care	Bed-day	Recipient	852.00	852.00	*Reference Costs 2013/2014*[49]
***GP visits* (if needed)**					
Out-of-surgery visit	Visit	Recipient	85.00	85.00	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Surgery visit	Visit	Recipient	34.00	34.00	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
Transplant centre advice	Call	Recipient	34.00	34.00	PSSRU's *Unit Costs of Health and Social Care 2014*[51]
***Unplanned hospital admission* (if needed)**					
Treatment					
Aciclovir (as sodium), 25 mg/ml	20-ml vial	Recipient	19.61	19.61	BNF 2014[50]
Aciclovir, 400 mg	56-tablet pack	Recipient	4.05	4.05	BNF 2014[50]

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Adrenaline (base), 100 µg/ml (1 in 10,000)	10-ml pre-filled disposable injection	Recipient	6.99	6.99	BNF 2014[50]
Amiodarone hydrochloride, 30 mg/ml	10-ml pre-filled disposable injection	Recipient	13.50	13.50	BNF 2014[50]
Amoxicillin (as sodium), 500 mg; and clavulanic acid (as potassium), 125 mg (co-amoxiclav)	500-/100-mg vial	Recipient	1.21	1.21	BNF 2014[50]
Amphotericin B	50-mg vial	Recipient	3.80	3.80	BNF 2014[50]
Aspirin, 300 mg	32-tablet pack	Recipient	3.35	3.35	BNF 2014[50]
Azathioprine, 25 mg	28-tablet pack	Recipient	3.24	3.24	BNF 2014[50]
Azithromycin (as dihydrate), 250 mg	4-capsule pack	Recipient	10.06	10.06	BNF 2014[50]
Aztreonam	1-g vial	Recipient	9.40	9.40	BNF 2014[50]
Balloon dilatation	Procedure	Recipient	4580.36	4580.36	*Reference Costs 2013/2014*[49]
Basiliximab	20-mg vial	Recipient	842.38	842.38	BNF 2014[50]
Bisoprolol fumarate, 10 mg	28-tablet pack	Recipient	1.02	1.02	BNF 2014[50]
Bortezomib	3.5-mg vial	Recipient	762.38	762.38	BNF 2014[50]
Bronchoscopy	Procedure	Recipient	340.00	340.00	BNF 2014[50]
Budesonide, 100 µg; and formoterol fumarate dihydrate, 6 µg (Symbicort 100/6 Turbohaler)	120-dose unit inhaler	Recipient	33.00	33.00	BNF 2014[50]
Calcium gluconate, 1 g	28-tablet pack	Recipient	15.68	15.68	BNF 2014[50]
Calcium polystyrene sulfonate [Calcium Resonium® (Aventis Pharma Ltd, Mumbai, India)]	300-g powder	Recipient	68.47	68.47	BNF 2014[50]
Candesartan cilexetil, 4 mg	28-tablet pack	Recipient	1.10	1.10	BNF 2014[50]
Caspofungin (as acetate)	70-mg vial	Recipient	416.78	416.78	BNF 2014[50]
Ciclosporin, 100 mg	30-capsule pack	Recipient	48.50	48.50	BNF 2014[50]
Ciclosporin, 50 mg/ml	5-ml ampoule	Recipient	9.16	9.16	BNF 2014[50]
Ciprofloxacin (as hydrochloride), 500 mg	20-tablet pack	Recipient	1.47	1.47	BNF 2014[50]
Clarithromycin	500-mg vial	Recipient	9.45	9.45	BNF 2014[50]
Clinical diagnosis/biopsy	Procedure	Recipient	295.00	295.00	*Reference Costs 2013/2014*[49]
Colistimethate sodium	1-million-unit vial	Recipient	5.60	5.60	BNF 2014[50]
Colistimethate sodium	2-million-unit vial	Recipient	3.24	3.24	BNF 2014[50]

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Computerised tomography	Procedure	Recipient	91.00	91.00	*Reference Costs 2013/2014*[49]
DeBakey tissue forceps	Forceps	Recipient	0.08	0.08	EAC
Docusate sodium, 100 mg	30-capsule pack	Recipient	2.09	2.09	BNF 2014[50]
Doxazosin (as mesilate), 4 mg	28-tablet pack	Recipient	1.04	1.04	BNF 2014[50]
Doxycycline (as hyclate), 100 mg	8-capsule pack	Recipient	1.13	1.13	BNF 2014[50]
ECG	24-hour test	Recipient	20.81	20.81	NuTH's costing tool[99]
Enoxaparin sodium [Clexane® Forte (Sanofi SA, Gentilly, France)], 150 mg	1-ml pre-filled disposable injection	Recipient	9.99	9.99	BNF 2014[50]
ECMO	Machine	Recipient	34,000.00	34,000.00	Tanveer Butt, NuTH, June 2015, personal communication
Filgrastim, 30 million units (300 µg /ml)	1-ml vial	Recipient	52.70	52.70	BNF 2014[50]
Flucloxacillin (as sodium)	1-g vial	Recipient	4.90	4.90	BNF 2014[50]
Fluticasone propionate, 250 µg; and salmeterol xinafoate, 50 µg [Seretide® 250 Accuhaler® (GlaxoSmithKline, Brentford, London, UK)]	120-unit dose inhaler	Recipient	35.00	35.00	BNF 2014[50]
Foscarnet sodium, 24 mg/ml	250-ml solution for infusion bottle	Recipient	119.85	119.85	BNF 2014[50]
Furosemide, 10 mg/ml	5-ml ampoule	Recipient	0.32	0.32	BNF 2014[50]
Ganciclovir (as sodium)	500-mg vial	Recipient	29.77	29.77	BNF 2014[50]
Gastrografin	Solution	Recipient	3.42	3.42	Medical supplies
Glucose anhydrous, 50 mg/ml	1000-ml bag	Recipient	1.38	1.38	BNF 2014[50]
iLA	Device	Recipient	4.28	4.28	EAC
Immunoglobulin	10-g vial	Recipient	408.00	408.00	BNF 2014[50]
Insulin, 3 ml	5 × 3-ml pre-filled disposable injection devices	Recipient	44.85	44.85	BNF 2014[50]
Intubation	Procedure	Recipient	235.00	235.00	*Reference Costs 2013/2014*[49]
Hydralazine hydrochloride, 50 mg	56-tablet pack	Recipient	18.30	18.30	BNF 2014[50]
Hydrocortisone (as sodium succinate)	100-mg vial	Recipient	1.16	1.16	BNF 2014[50]
Lansoprazole, 30 mg	28-capsule pack	Recipient	1.52	1.52	BNF 2014[50]

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Level 1 ward care (hospital stay)	Bed-day	Recipient	265.00	265.00	*Reference Costs 2013/2014*[49]
Macrogol compound oral powder	50-sachet pack	Recipient	11.13	11.13	BNF 2014[50]
Magnesium hydroxide with liquid paraffin	150-ml bottle	Recipient	11.50	11.50	BNF 2014[50]
Magnesium sulfate heptahydrate, 100 mg	10-ml ampoule	Recipient	51.93	51.93	BNF 2014[50]
Magnetic resonance imaging scan	Test	Recipient	412.00	412.00	*Reference Costs 2013/2014*[49]
Meropenem (as trihydrate)	1-g vial	Recipient	16.00	16.00	BNF 2014[50]
Methylprednisolone (as sodium succinate)	500-mg vial	Recipient	9.60	9.60	BNF 2014[50]
Methylprednisolone (as sodium succinate)	1-g vial	Recipient	17.30	17.30	BNF 2014[50]
Metoclopramide hydrochloride, 5 mg/ml	2-ml ampoule	Recipient	0.32	0.32	BNF 2014[50]
Midazolam (as hydrochloride), 1 mg/ml	5-ml ampoule	Recipient	0.65	0.65	BNF 2014[50]
Minocycline (as hydrochloride), 100 mg	28-tablet pack	Recipient	13.09	13.09	BNF 2014[50]
Moxifloxacin (as hydrochloride), 1.6 mg/ml	250-ml solution for infusion bottle	Recipient	39.95	39.95	BNF 2014[50]
Nefopam hydrochloride, 30 mg	90-tablet pack	Recipient	10.59	10.59	BNF 2014[50]
Non-invasive ventilation	Procedure	Recipient	166.00	166.00	BNF 2014[50]
Normal immunoglobulin, 10 g	200-ml solution for infusion bottle	Recipient	408.00	408.00	BNF 2014[50]
Oxycodone hydrochloride, 10 mg/ml	120-ml oral solution	Recipient	46.63	46.63	BNF 2014[50]
Packed red blood cells	274-ml bag	Recipient	120.00	120.00	Paul Henderson, NuTH, September 2014, personal communication/ Yvonne Scott, NuTH, July 2015, personal communication
Phosphate enema	133-ml enema pack	Recipient	0.68	0.68	BNF 2014[50]
Piperacillin (as sodium), 4 g; and tazobactam (as sodium), 500 mg (Tazocin)	4.5-g vial	Recipient	15.17	15.17	BNF 2014[50]
Posaconazole, 100 mg	96-tablet pack	Recipient	2387.85	2387.85	BNF 2014[50]
Prednisolone, 5 mg	28-tablet pack	Recipient	1.29	1.29	BNF 2014[50]

continued

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Pregabalin, 150 mg	56-capsule pack	Recipient	65.40	65.40	BNF 2014[50]
Redo lung transplantation	Procedure	Recipient	2702.00	2702.00	*Reference Costs 2013/2014*[49]
Renal support	Treatment	Recipient	755.04	755.04	*Reference Costs 2013/2014*[49]
Ribavirin, 200 mg	42-tablet pack	Recipient	92.50	92.50	BNF 2014[50]
Ribavirin, 400 mg	56-tablet pack	Recipient	246.65	246.65	BNF 2014[50]
Salbutamol (as sulfate), 5 mg/2.5 ml	20-unit dose nebuliser liquid vial	Recipient	3.82	3.82	BNF 2014[50]
Sirolimus, 2 mg	30-tablet pack	Recipient	172.98	172.98	BNF 2014[50]
Sodium bicarbonate, 42 mg/ml	500-ml intravenous infusion bottle	Recipient	9.39	9.39	BNF 2014[50]
2 l of 0.9% sodium chloride solution	1-l solution	Recipient	0.97	0.97	BNF 2014[50]
Stenting	Procedure	Recipient	4580.36	4580.36	*Reference Costs 2013/2014*[49]
Sulfamethoxazole, 80 mg; and trimethoprim, 16 mg (Septrin)	5-ml ampoule	Recipient	1.78	1.78	BNF 2014[50]
Sulfamethoxazole, 400 mg; and trimethoprim, 80 mg (co-trimoxazole)	5 ml ampoule	Recipient	1.78	1.78	BNF 2014[50]
Surgical intervention	Procedure	Recipient	4580.36	4580.36	*Reference Costs 2013/2014*[49]
Tacrolimus (Prograf), 1 mg	50-capsule pack	Recipient	80.28	80.28	BNF 2014[50]
Tacrolimus (Prograf), 1 mg	100-capsule pack	Recipient	160.54	160.54	BNF 2014[50]
Tacrolimus (Prograf), 5 mg/ml	10 × 1-ml ampoules	Recipient	58.45	58.45	BNF 2014[50]
Tinzaparin sodium, 20,000 units/ml [Innohep® (Leo Pharma A/S, Copenhagen, Denmark)	0.5-ml vial	Recipient	5.95	5.95	BNF 2014[50]
Tracheostomy	Procedure	Recipient	135.00	135.00	*Reference Costs 2013/2014*[49]
Tramadol hydrochloride, 150 mg	60-capsule pack	Recipient	22.92	22.92	BNF 2014[50]
Ultrasound scan	Test	Recipient	59.00	59.00	*Reference Costs 2013/2014*[49]
Valganciclovir (as hydrochloride), 450 mg	60-tablet pack	Recipient	1081.46	1081.46	BNF 2014[50]
Vancomycin (as hydrochloride), 125 mg	28-capsule pack	Recipient	140.08	140.08	BNF 2014[50]
Voriconazole	200-mg vial	Recipient	77.14	77.14	BNF 2014[50]

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Warfarin sodium, 3 mg	28-tablet pack	Recipient	1.07	1.07	BNF 2014[50]
Warfarin sodium, 1 mg/ml	150-ml oral suspension	Recipient	107.98	107.98	BNF 2014[50]
Ward usage					
HDU care	Bed-day	Recipient	852.00	852.00	*Reference Costs 2013/2014*[49]
ITU care	Bed-day	Recipient	852.00	852.00	*Reference Costs 2013/2014*[49]
***Immunosuppressive medications* (if needed)**					
Azathioprine, 25 mg	28-tablet pack	Recipient	3.24	3.24	BNF 2014[50]
Azathioprine, 50 mg	56-tablet pack	Recipient	3.48	3.48	BNF 2014[50]
Ciclosporin, 25 mg	30-capsule pack	Recipient	13.05	13.05	BNF 2014[50]
Ciclosporin, 50 mg	30-capsule pack	Recipient	25.50	25.50	BNF 2014[50]
Ciclosporin, 100 mg	30-capsule pack	Recipient	48.50	48.50	BNF 2014[50]
Mycophenolate mofetil, 500 mg	50-tablet pack	Recipient	10.15	10.15	BNF 2014[50]
Prednisolone, 1 mg	28-tablet pack	Recipient	1.08	1.08	BNF 2014[50]
Prednisolone, 5 mg	28-tablet pack	Recipient	1.29	1.29	BNF 2014[50]
Prednisolone, 25 mg	56-tablet pack	Recipient	50.00	50.00	BNF 2014[50]
Prednisolone acetate, 25 mg/ml	1 ml ampoule	Recipient	6.87	6.87	BNF 2014[50]
Sirolimus, 500 µg	30-tablet pack	Recipient	69.00	69.00	BNF 2014[50]
Sirolimus, 1 mg	30-tablet pack	Recipient	86.49	86.49	BNF 2014[50]
Sirolimus, 2 mg	30-tablet pack	Recipient	172.98	172.98	BNF 2014[50]
Tacrolimus, 500 µg	50-capsule pack	Recipient	61.88	61.88	BNF 2014[50]
Tacrolimus, 1 mg	50-capsule pack	Recipient	80.28	80.28	BNF 2014[50]
Tacrolimus, 1 mg	100-capsule pack	Recipient	160.54	160.54	BNF 2014[50]
Tacrolimus, 5 mg	50-capsule pack	Recipient	296.58	296.58	BNF 2014[50]
Other					
Aciclovir, 200 mg	25-tablet pack	Recipient	1.77	1.77	BNF 2014[50]
Amoxicillin (as trihydrate), 500 mg	21-capsule pack	Recipient	1.62	1.62	BNF 2014[50]
Azithromycin (as dihydrate), 250 mg	4-capsule pack	Recipient	10.06	10.06	BNF 2014[50]
Beclomethasone dipropionate, 400 µg/dose	100-dose unit	Recipient	19.61	19.61	BNF 2014[50]
Calcium carbonate (Adcal), 1.5 g	100-tablet pack	Recipient	8.70	8.70	BNF 2014[50]

continued

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Cetirizine hydrochloride, 10 mg	30-tablet pack	Recipient	1.07	1.07	BNF 2014[50]
Ciclosporin (NEORAL), 10 mg	60-capsule pack	Recipient	16.68	16.68	BNF 2014[50]
Ciclosporin (NEORAL), 25 mg	30-capsule pack	Recipient	16.79	16.79	BNF 2014[50]
Ciclosporin (NEORAL), 50 mg	50-capsule pack	Recipient	32.88	32.88	BNF 2014[50]
Ciclosporin, 100 mg	30-capsule pack	Recipient	62.41	62.41	BNF 2014[50]
Citalopram (as hydrobromide), 20 mg	28-tablet pack	Recipient	1.09	1.09	BNF 2014[50]
Dapsone, 100 mg	28-tablet pack	Recipient	92.51	92.51	BNF 2014[50]
Dexamethasone, 2 mg	50-tablet pack	Recipient	52.41	52.41	BNF 2014[50]
Doxycycline (as hyclate), 100 mg	8-capsule pack	Recipient	1.13	1.13	BNF 2014[50]
Furosemide, 40 mg	28-tablet pack	Recipient	0.88	0.88	BNF 2014[50]
Hydrocortisone, 10 mg	30-tablet pack	Recipient	65.78	65.78	BNF 2014[50]
Hydrocortisone, 20 mg	30-tablet pack	Recipient	86.63	86.63	BNF 2014[50]
Lisinopril dihydrate, 2.5 mg	28-tablet pack	Recipient	0.96	0.96	BNF 2014[50]
Lisinopril dihydrate, 5 mg	28-tablet pack	Recipient	0.98	0.98	BNF 2014[50]
Methylprednisolone, 2 mg	30-tablet pack	Recipient	3.88	3.88	BNF 2014[50]
Methylprednisolone (as sodium succinate)	40-mg vial	Recipient	1.58	1.58	BNF 2014[50]
Methylprednisolone (as sodium succinate)	1-g vial	Recipient	17.3	17.3	BNF 2014[50]
Mycophenolic acid (as sodium), 180 mg	120-tablet pack	Recipient	96.72	96.72	BNF 2014[50]
Mycophenolic acid (as sodium), 360 mg	120-tablet pack	Recipient	193.43	193.43	BNF 2014[50]
N-acetylcysteine, 200 mg/ml	10-ml ampoule	Recipient	1.96	1.96	BNF 2014[50]
Perindopril erbumine, 2 mg	30-tablet pack	Recipient	1.15	1.15	BNF 2014[50]
Perindopril erbumine, 4 mg	30-tablet pack	Recipient	1.56	1.56	BNF 2014[50]
Sulfamethoxazole, 400 mg; and trimethoprim, 80 mg (co-trimoxazole)	28-tablet pack	Recipient	3.34	3.34	BNF 2014[50]
Tacrolimus (Prograf), 1 mg	50-capsule pack	Recipient	80.28	80.28	BNF 2014[50]
Tacrolimus (Prograf), 1 mg	100-capsule pack	Recipient	160.54	160.54	BNF 2014[50]
Tinzaparin sodium, 3500 units	0.35-ml pre-filled disposable injection	Recipient	2.77	2.77	BNF 2014[50]

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Concomitant medications *Variable costs*					
Treatment					
Aciclovir, 200 mg	25-tablet pack	Recipient	1.77	1.77	BNF 2014[50]
Adrenaline (base), 100 µg/ml (1 in 10,000)	10-ml pre-filled disposable injection	Recipient	6.99	6.99	BNF 2014[50]
Alendronic acid (as sodium), 70 mg	28-tablet pack	Recipient	1.03	1.03	BNF 2014[50]
Alfentanil (as hydrochloride), 500 µg/ml	2-ml ampoule	Recipient	0.7	0.7	BNF 2014[50]
Alfentanil (as hydrochloride), 5 mg/ml	1-ml ampoule	Recipient	2.5	2.5	BNF 2014[50]
Allopurinol, 300 mg	28-tablet pack	Recipient	1.18	1.18	BNF 2014[50]
Amiloride hydrochloride, 5 mg; and furosemide, 40 mg (co-amilofruse)	56-tablet pack	Recipient	2.50	2.50	BNF 2014[50]
Amiodarone hydrochloride, 30 mg/ml	10-ml pre-filled disposable syringe	Recipient	13.5	13.5	BNF 2014[50]
Amiodarone hydrochloride, 100 mg	28-tablet pack	Recipient	1.08	1.08	BNF 2014[50]
Amiodarone hydrochloride, 200 mg	28-tablet pack	Recipient	2.04	2.04	BNF 2014[50]
Amitriptyline hydrochloride, 10 mg	28-tablet pack	Recipient	1.19	1.19	BNF 2014[50]
Amlodipine, 5 mg	28-tablet pack	Recipient	0.98	0.98	BNF 2014[50]
Amlodipine, 10 mg	28-tablet pack	Recipient	1.00	1.00	BNF 2014[50]
Amoxicillin (as trihydrate), 500 mg	21-capsule pack	Recipient	1.62	1.62	BNF 2014[50]
Amoxicillin (as amoxicillin trihydrate), 500 mg; and clavulanic acid (as potassium), 125 mg	21-tablet pack	Recipient	9.60	9.60	BNF 2014[50]
Amphotericin B, 5 mg/ml	20-lozenge pack	Recipient	7.84	7.84	BNF 2014[50]
Amphotericin B (as phospholipid complex), 5 mg/ml	20-ml vial	Recipient	77.50	77.50	BNF 2014[50]
Antiembolism socks	Socks pack	Recipient	12.99	12.99	Medical supplies
Anti-thymocyte immunoglobulin (rabbit)	25-mg vial	Recipient	158.77	158.77	BNF 2014[50]
Aspirin, 75 mg	28-tablet pack	Recipient	0.94	0.94	BNF 2014[50]
Atracurium besilate, 10 mg/ml	5-ml ampoule	Recipient	4.00	4.00	BNF 2014[50]
Azathioprine, 25 mg	28-tablet pack	Recipient	3.24	3.24	BNF 2014[50]
Azathioprine, 50 mg	56-tablet pack	Recipient	3.48	3.48	BNF 2014[50]

continued

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Azithromycin (as dihydrate), 250 mg	4-tablet pack	Recipient	1.83	1.83	BNF 2014[50]
Azithromycin (as dihydrate), 250 mg	6-capsule pack	Recipient	15.10	15.10	BNF 2014[50]
Azithromycin, 500 mg	3-tablet pack	Recipient	1.77	1.77	BNF 2014[50]
Aztreonam	2-g vial	Recipient	18.82	18.82	BNF 2014[50]
Bisoprolol fumarate, 1.25 mg	28-tablet pack	Recipient	2.35	2.35	BNF 2014[50]
Bisoprolol fumarate, 2.5 mg	28-tablet pack	Recipient	2.35	2.35	BNF 2014[50]
Bisoprolol fumarate, 5 mg	28-tablet pack	Recipient	0.98	0.98	BNF 2014[50]
Bupivacaine hydrochloride, 1 mg/ml	100-ml infusion bag	Recipient	8.41	8.41	BNF 2014[50]
Calcium carbonate (Adcal), 1.5 g	100-tablet pack	Recipient	8.70	8.70	BNF 2014[50]
Calcium carbonate, 1.25 g; and colecalciferol, 400 units (Calcichew D3 Forte)	60-tablet pack	Recipient	4.24	4.24	BNF 2014[50]
Calcium chloride dihydrate, 10%	10-ml pre-filed disposable injection	Recipient	6.94	6.94	BNF 2014[50]
Calogen® (Nutricia, Danone, Paris, France) emulsion	500-ml bottle	Recipient	10.72	10.72	BNF 2014[50]
Carbocisteine, 375 mg	120-capsule pack	Recipient	17.11	17.11	BNF 2014[50]
Caspofungin (as acetate)	50-mg vial	Recipient	327.67	327.67	BNF 2014[50]
Ceftazidime (as pentahydrate)	2-g vial	Recipient	17.90	17.90	BNF 2014[50]
Chlordiazepoxide hydrochloride, 5 mg	100-capsule pack	Recipient	8.07	8.07	BNF 2014[50]
Chlordiazepoxide hydrochloride [Librium Meda AB, Solna, Sweden)], 10 mg	100-capsule pack	Recipient	14.06	14.06	BNF 2014[50]
Chlorhexidine gluconate, 4%	500-ml surgical scrub	Recipient	3.59	3.59	BNF 2014[50]
Chlorhexidine hydrochloride	500-mg pump pack	Recipient	6.04	6.04	BNF 2014[50]
Chlorhexidine hydrochloride, 1mg/g; and neomycin sulfate, 5 mg/g [Naseptin® (Alliance Pharma, Clippenham, UK)]	15-g nasal cream	Recipient	1.90	1.90	BNF 2014[50]
Chlorhexidine hydrochloride, 10 mg/g; and nystatin, 100,000 units/g [Nystaform® (Typharm Ltd, Norwich, UK)]	30-g cream	Recipient	2.62	2.62	BNF 2014[50]

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Chlorphenamine maleate, 10 mg/ml	1 ml ampoule	Recipient	4.47	4.47	BNF 2014[50]
Chlorpromazine hydrochloride, 25 mg	28-tablet pack	Recipient	2.31	2.31	BNF 2014[50]
Ciclosporin (NEORAL), 25 mg	30-capsule pack	Recipient	16.79	16.79	BNF 2014[50]
Ciclosporin, 50 mg	30-capsule pack	Recipient	25.50	25.50	BNF 2014[50]
Ciclosporin, 100 mg	30-capsule pack	Recipient	48.50	48.50	BNF 2014[50]
Ciprofloxacin (as hydrochloride), 500 mg (Ciproxin)	10-tablet pack	Recipient	12.49	12.49	BNF 2014[50]
Ciprofloxacin (as hydrochloride), 750 mg	10-tablet pack	Recipient	8.00	8.00	BNF 2014[50]
Citalopram (as hydrobromide), 20 mg	28-tablet pack	Recipient	1.09	1.09	BNF 2014[50]
Citalopram (as hydrobromide), 40 mg	28-tablet pack	Recipient	1.28	1.28	BNF 2014[50]
Clonidine hydrochloride, 25 µg	112-tablet pack	Recipient	5.02	5.02	BNF 2014[50]
Codeine phosphate, 8 mg; and paracetamol, 500 mg	30-tablet pack	Recipient	1.19	1.19	BNF 2014[50]
Codeine phosphate, 30 mg; and paracetamol, 500 mg	100-tablet pack	Recipient	5.80	5.80	BNF 2014[50]
Codeine phosphate, 30 mg	28-tablet pack	Recipient	1.52	1.52	BNF 2014[50]
Codeine phosphate, 60 mg	28-tablet pack	Recipient	2.70	2.70	BNF 2014[50]
Colecalciferol, 500 µg (20,000 units)	15-capsule pack	Recipient	17.40	17.40	BNF 2014[50]
Colistimethate sodium	1-million-unit vial	Recipient	3.24	3.24	BNF 2014[50]
Colistimethate sodium	2-million-unit vial	Recipient	3.24	3.24	BNF 2014[50]
CREON® (AbbVie Inc., North Chicago, IL, USA), 25,000 units	100-capsule pack	Recipient	28.25	28.25	BNF 2014[50]
CREON Micro Pancreatine, 20 g	60.12-mg granules	Recipient	31.50	31.50	BNF 2014[50]
Cryoprecipitate	8 units	Recipient	711.29	711.29	Medical supplies
Cyclizine hydrochloride, 50 mg	100-tablet pack	Recipient	10.97	10.97	BNF 2014[50]
Dapsone, 100 mg	28-tablet pack	Recipient	92.51	92.51	BNF 2014[50]

continued

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Diazepam, 2 mg	28-tablet pack	Recipient	1.09	1.09	BNF 2014[50]
Digoxin, 250 µg/ml	2-ml ampoule	Recipient	0.70	0.70	BNF 2014[50]
Diltiazem hydrochloride, 120 mg	28-capsule pack	Recipient	6.27	6.27	BNF 2014[50]
Diltiazem hydrochloride, 200 mg	7-capsule pack	Recipient	6.27	6.27	BNF 2014[50]
Docusate sodium, 100 mg	100-capsule pack	Recipient	6.98	6.98	BNF 2014[50]
Domperidone (as maleate), 10 mg	100-tablet pack	Recipient	4.83	4.83	BNF 2014[50]
Dopamine hydrochloride, 40 mg/ml	5-ml ampoule	Recipient	3.88	3.88	BNF 2014[50]
Dosulepin hydrochloride, 25 mg	28-capsule pack	Recipient	1.86	1.86	BNF 2014[50]
Doxazosin (as mesilate), 4 mg	28-tablet pack	Recipient	5.00	5.00	BNF 2014[50]
Doxycycline (as hyclate), 100 mg	8-capsule pack	Recipient	1.13	1.13	BNF 2014[50]
Enoxaparin sodium, 100 mg/ml	0.4-ml pre-filled disposable injection	Recipient	3.03	3.03	BNF 2014[50]
Ensure® (Abbott Laboratories, Chicago, IL, USA) liquid	250 ml	Recipient	2.26	2.26	BNF 2014[50]
Erythromycin (as lactobionate)	1-g vial	Recipient	10.98	10.98	BNF 2014[50]
Esomeprazole (as magnesium dihydrate), 40 mg	28-capsule pack	Recipient	3.96	3.96	BNF 2014[50]
Ethambutol hydrochloride, 400 mg	56-tablet pack	Recipient	42.74	42.74	BNF 2014[50]
Ezetimibe, 10 mg	28-tablet pack	Recipient	26.31	26.31	BNF 2014[50]
Ethinylestradiol, 30 µg; and gestodene, 75 µg	21-day preparation	Recipient	6.73	6.73	BNF 2014[50]
Ferrous sulfate dried, 200 mg	28-tablet pack	Recipient	1.11	1.11	BNF 2014[50]
Flucloxacillin (as sodium), 500 mg	28-capsule pack	Recipient	2.60	2.60	BNF 2014[50]
Flucloxacillin (as sodium)	1-g vial	Recipient	4.90	4.90	BNF 2014[50]
Fluconazole, 50 mg	7-capsule pack	Recipient	1.02	1.02	BNF 2014[50]
Fluconazole, 200 mg	7-capsule pack	Recipient	6.36	6.36	BNF 2014[50]
Fluconazole, 2 mg/ml	100-ml solution for infusion bottle	Recipient	27.45	27.45	BNF 2014[50]
Fluoxetine (as hydrochloride), 20 mg	30-capsule pack	Recipient	1.16	1.16	BNF 2014[50]
Fluticasone propionate, 50 µg	150-unit dose nasal spray	Recipient	11.01	11.01	BNF 2014[50]

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Fluticasone propionate, 250 µg (Flixotide 250 Accuhale)	60-dose inhaler	Recipient	21.26	21.26	BNF 2014[50]
Fluticasone propionate, 250 µg; and salmeterol xinafoate, 50 µg (Seretide 250 Accuhaler)	60-dose inhaler	Recipient	35.00	35.00	BNF 2014[50]
Folic acid, 400 µg	90-tablet pack	Recipient	2.71	2.71	BNF 2014[50]
Foscarnet sodium, 24 mg/ml	250-ml solution for infusion bottle	Recipient	119.85	119.85	BNF 2014[50]
Fosfomycin (as sodium)	2-g vial	Recipient	15.00	15.00	BNF 2014[50]
Fresh-frozen plasma	271-ml bag	Recipient	28.46	28.46	NHSBT
Furosemide, 10 mg/ml	2-ml ampoule	Recipient	0.35	0.35	BNF 2014[50]
Furosemide, 20 mg	28-tablet pack	Recipient	0.98	0.98	BNF 2014[50]
Furosemide, 40 mg	28-tablet pack	Recipient	0.88	0.88	BNF 2014[50]
Ganciclovir (as sodium)	500-mg vial	Recipient	29.77	29.77	BNF 2014[50]
Gelatin (Gelofusine®)	1-l infusion bag	Recipient	9.04	9.04	BNF 2014[50]
Gelatin, 140 mg/g; and glycerol, 700 mg/g	4-g supplementary pack	Recipient	1.94	1.94	BNF 2014[50]
Gliclazide (glycoside), 30 mg	56-tablet pack	Recipient	4.10	4.10	BNF 2014[50]
Gliclazide, 40 mg	28-tablet pack	Recipient	3.36	3.36	BNF 2014[50]
Glucose anhydrous, 500 mg/ml	50-ml vial	Recipient	2.01	2.01	BNF 2014[50]
Glyceryl trinitrate (GTN), 1 mg/ml	50-ml ampoule	Recipient	15.90	15.90	BNF 2014[50]
Haloperidol, 5 mg	28-tablet pack	Recipient	3.30	3.30	BNF 2014[50]
Haloperidol, 5 mg/ml	1-ml ampoule	Recipient	0.87	0.87	BNF 2014[50]
Heparin sodium, 5000 units/ml	1-ml ampoule	Recipient	2.90	2.90	BNF 2014[50]
Heparin sodium, 5000 units/ml	5-ml ampoule	Recipient	7.58	7.58	BNF 2014[50]
Hydroxocobalamin, 1 mg/ml	1-ml ampoule	Recipient	1.75	1.75	BNF 2014[50]
Hyoscine butylbromide [Buscopan® (Boehringer Ingelheim, Ingelheim, Germany)], 10 mg	56-tablet pack	Recipient	3.00	3.00	BNF 2014[50]
Ibandronic acid (as sodium monohydrate) 50 mg	28-tablet pack	Recipient	10.76	10.76	BNF 2014[50]
Iloprost (as THAM), 10 µg/ml	30 × 1-ml unit dose vials	Recipient	400.19	400.19	BNF 2014[50]

continued

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Insulin, 3 ml	5 × 3-ml pre-filled disposable injection devices	Recipient	44.85	44.85	BNF 2014[50]
Insulin aspart, 100 units/ml	5 × 3-ml pre-filled disposable injection devices	Recipient	32.13	32.13	BNF 2014[50]
Insulin human (as soluble human) (ACTRAPID®), 100 units/ml	10-ml vial	Recipient	7.48	7.48	BNF 2014[50]
Insulin human (as detemir), 100 units/ml (LEMEVIR®, Novo Nordisk, Bagsværd, Denmark)	5 × 3-ml pre-filled disposable injection device	Recipient	43.00	43.00	BNF 2014[50]
Ipratropium bromide, 250 µg/ml	60 × 1-ml unit dose vial	Recipient	12.44	12.44	BNF 2014[50]
Ipratropium bromide	500-µg nebuliser solution	Recipient	23.75	23.75	BNF 2014[50]
Ipratropium bromide, 2.5 mg/2.5 ml	60-unit dose vial	Recipient	24.10	24.10	BNF 2014[50]
Ipratropium bromide, 200 µg/ml; and salbutamol (as sulfate), 1 mg/ml (Combivent)	60-unit dose vials	Recipient	24.10	24.10	BNF 2014[50]
Itraconazole, 100 mg	15-capsule pack	Recipient	4.57	4.57	BNF 2014[50]
Itraconazole, 10 mg/ml	150-ml oral solution	Recipient	58.34	58.34	BNF 2014[50]
Labetalol hydrochloride, 100 mg	56-tablet pack	Recipient	6.99	6.99	BNF 2014[50]
Labetalol hydrochloride, 200 mg	56-tablet pack	Recipient	9.89	9.89	BNF 2014[50]
Lactulose	300-ml solution	Recipient	1.95	1.95	BNF 2014[50]
Lansoprazole, 15 mg	28-capsule pack	Recipient	1.17	1.17	BNF 2014[50]
Lansoprazole, 30 mg	28-tablet pack	Recipient	1.52	1.52	BNF 2014[50]
Loratadine, 10 mg	30-tablet pack	Recipient	1.11	1.11	BNF 2014[50]
Levomepromazine maleate, 25 mg	84-tablet pack	Recipient	20.26	20.26	BNF 2014[50]
Linezolid, 600 mg	10-tablet pack	Recipient	445.00	445.00	BNF 2014[50]
Loperamide hydrochloride, 2 mg	30-tablet pack	Recipient	2.15	2.15	BNF 2014[50]
Lorazepam, 1 mg	28-tablet pack	Recipient	2.67	2.67	BNF 2014[50]
Lymecycline, 408 mg	28-capsule pack	Recipient	9.18	9.18	BNF 2014[50]

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Magnesium oxide, 160 mg	28-capsule pack	Recipient	17.50	17.50	Medical supplies
Magnesium sulfate heptahydrate, 500 mg/ml	2-ml ampoule	Recipient	1.18	1.18	BNF 2014[50]
Magnesium sulfate heptahydrate, 500 mg/ml	5-ml ampoule	Recipient	5.56	5.56	BNF 2014[50]
Magnesium sulfate heptahydrate, 500 mg/ml	4-ml ampoule	Recipient	10.23	10.23	BNF 2014[50]
Menadiol phosphate (as sodium phosphate), 10 mg	100-tablet pack	Recipient	128.60	128.60	BNF 2014[50]
Meropenem (as trihydrate)	1-g vial	Recipient	16.00	16.00	BNF 2014[50]
Methylprednisolone (as sodium succinate)	500-mg vial	Recipient	9.60	9.60	BNF 2014[50]
Methylprednisolone (as sodium succinate)	1-g vial	Recipient	17.30	17.30	BNF 2014[50]
Metformin hydrochloride, 500 mg	28-tablet pack	Recipient	2.66	2.66	BNF 2014[50]
Metoclopramide hydrochloride, 10 mg	28-tablet pack	Recipient	0.97	0.97	BNF 2014[50]
Metronidazole, 400 mg	21-tablet pack	Recipient	1.70	1.70	BNF 2014[50]
Midazolam (as hydrochloride), 1 mg/ml	5-ml ampoule	Recipient	6.00	6.00	BNF 2014[50]
Milrinone (as lactate), 1 mg/ml	10-ml ampoule	Recipient	19.91	19.91	BNF 2014[50]
Minocycline (as hydrochloride), 100 mg	28-tablet pack	Recipient	6.20	6.20	BNF 2014[50]
Mirtazapine, 30 mg	28-tablet pack	Recipient	1.60	1.60	BNF 2014[50]
Montelukast (as sodium), 10 mg	28-tablet pack	Recipient	26.97	26.97	BNF 2014[50]
Mometasone furoate, 50 µg	140-unit dose nasal spray	Recipient	7.68	7.68	BNF 2014[50]
Morphine sulfate, 1 mg/ml	10-mg disposable syringe	Recipient	15.00	15.00	BNF 2014[50]
Morphine sulfate (Oramorph®), 10 mg/5 ml	300-ml oral solution	Recipient	5.45	5.45	BNF 2014[50]
Movicol® (Norgine Pharmaceuticals Ltd, Amsterdam, the Netherlands)	30-sachet pack	Recipient	6.68	6.68	BNF 2014[50]
Moxifloxacin (as hydrochloride), 400 mg	5-tablet pack	Recipient	12.43	12.43	BNF 2014[50]
Multivitamins	28-capsule pack	Recipient	1.50	1.50	BNF 2014[50]
Mupirocin, 20 mg/g	15-g ointment	Recipient	5.35	5.35	BNF 2014[50]

continued

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Micafungin (as sodium)	100-mg vial	Recipient	341.00	341.00	BNF 2014[50]
N-acetylcysteine, 600 mg	100-tablet pack	Recipient	23.45	23.45	Medical supplies
Naproxen, 500 mg	28-tablet pack	Recipient	1.67	1.67	BNF 2014[50]
Nebivolol (as hydrochloride), 5 mg	28-tablet pack	Recipient	1.81	1.81	BNF 2014[50]
Nifedipine, 5 mg	84-capsule pack	Recipient	15.20	15.20	BNF 2014[50]
Nifedipine, 10 mg	84-capsule pack	Recipient	6.53	6.53	BNF 2014[50]
Noradrenaline base, 1 mg/ml (as noradrenaline acid tartrate, 2 mg/ml)	4-ml ampoule	Recipient	4.40	4.40	BNF 2014[50]
Nutrison energy multifibre	1000-ml solution	Recipient	11.74	11.74	BNF 2014[50]
Nystatin, 100,000 units/ml	30-ml oral suspension	Recipient	3.35	3.35	BNF 2014[50]
Omeprazole (as magnesium), 10 mg	28-tablet pack	Recipient	1.25	1.25	BNF 2014[50]
Omeprazole (as magnesium), 20 mg	28-tablet pack	Recipient	6.11	6.11	BNF 2014[50]
Omeprazole (as magnesium), 40 mg	28-capsule pack	Recipient	4.98	4.98	BNF 2014[50]
Omeprazole (as sodium)	40-mg vial	Recipient	4.16	4.16	BNF 2014[50]
Ondansetrol (as hydrochloride), 2 mg/ml	1-ml ampoule	Recipient	1.00	1.00	BNF 2014[50]
Ondansetron (as hydrochloride), 4 mg	30-tablet pack	Recipient	5.37	5.37	BNF 2014[50]
Oxycodone hydrochloride, 5 mg	56-tablet pack	Recipient	11.43	11.43	BNF 2014[50]
Oxycodone hydrochloride, 10 mg	56-capsule pack	Recipient	22.86	22.86	BNF 2014[50]
Pabrinex® (Archimedes Pharma Ltd, Reading, UK) vitamin B substances with ascorbic acid, 250 mg/10 ml	2 × 5 ml ampoule	Recipient	2.25	2.25	BNF 2014[50]
Packed red blood cells	274-ml bag	Recipient	120.00	120.00	Paul Henderson, NuTH, September 2014, personal communication/ Yvonne Scott, NuTH, July 2015, personal communication
Paracetamol, 500 mg	32-tablet pack	Recipient	0.96	0.96	BNF 2014[50]
Paracetamol, 1 g	10 mg/ml 100-ml vial	Recipient	1.20	1.20	BNF 2014[50]
Peppermint water	100-ml solution	Recipient	10.81	10.81	BNF 2014[50]

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Perindopril erbumine, 4 mg	30-tablet pack	Recipient	1.56	1.56	BNF 2014[50]
Phenoxymethylpenicillin (as potassium), 250 mg	28-tablet pack	Recipient	1.20	1.20	BNF 2014[50]
Phosphate	500-ml bottle	Recipient	5.15	5.15	BNF 2014[50]
Piperacillin,(as sodium) 4 g; and tazobactam (as sodium), 500 mg (Tazocin)	4.5-g vial	Recipient	15.17	15.17	BNF 2014[50]
Platelets	250-ml bag	Recipient	196.96	196.96	BNF 2014[50]
Posaconazole, 100 mg	96-tablet pack	Recipient	2387.85	2387.85	BNF 2014[50]
Potassium bicarbonate, 400 mg; and potassium chloride, 600 mg [Sando-K® (HK Pharma Ltd, Bedford, UK)]	20 tablets	Recipient	1.53	1.53	BNF 2014[50]
Potassium chloride, 150 mg/ml	10-ml ampoule	Recipient	0.48	0.48	BNF 2014[50]
Pravastatin sodium, 10 mg	28-tablet pack	Recipient	1.31	1.31	BNF 2014[50]
Pravastatin sodium, 20 mg	28-tablet pack	Recipient	1.57	1.57	BNF 2014[50]
Pravastatin sodium, 40 mg	28-tablet pack	Recipient	1.93	1.93	BNF 2014[50]
Prednisolone, 5 mg	28-tablet pack	Recipient	1.29	1.29	BNF 2014[50]
Pregabalin, 25 mg	56-capsule pack	Recipient	64.40	64.40	BNF 2014[50]
Pregabalin, 50 mg	84-capsule pack	Recipient	96.60	96.60	BNF 2014[50]
Pregabalin, 75 g	56-capsule pack	Recipient	64.40	64.40	BNF 2014[50]
Pregabalin, 100 mg	84-capsule pack	Recipient	96.60	96.60	BNF 2014[50]
Prochlorperazine maleate, 3 mg	5 × 10-tablet pack	Recipient	6.49	6.49	BNF 2014[50]
Propofol, 5 mg/ml	20-ml ampoule	Recipient	3.46	3.46	BNF 2014[50]
Propofol, 10 mg/ml	20-ml ampoule	Recipient	3.07	3.07	BNF 2014[50]
Propofol, 10 mg/ml	50-ml pre-filled disposable injection	Recipient	10.10	10.10	BNF 2014[50]
Ramipril, 2.5 mg	28-tablet pack	Recipient	1.12	1.12	BNF 2014[50]
Ramipril, 5 mg	28-capsule pack	Recipient	1.24	1.24	BNF 2014[50]
Ranitidine (as hydrochloride), 25 mg/ml	2-ml ampoule	Recipient	0.54	0.54	BNF 2014[50]
Ranitidine (as hydrochloride), 150 mg	60-tablet pack	Recipient	1.57	1.57	BNF 2014[50]

continued

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Ranitidine (as hydrochloride), 300 mg	30-tablet pack	Recipient	1.48	1.48	BNF 2014[50]
Remifentanil (as hydrochloride)	5-mg vial	Recipient	25.40	25.40	BNF 2014[50]
Risperidone, 500 µg	20-tablet pack	Recipient	1.07	1.07	BNF 2014[50]
Risperidone, 2 mg	60-tablet pack	Recipient	1.68	1.68	BNF 2014[50]
Salbutamol (as sulfate), 2.5 mg/2.5 ml	20-unit dose nebuliser	Recipient	1.91	1.91	BNF 2014[50]
Salbutamol (as sulfate), 200 µg	100-dose unit inhaler	Recipient	4.85	4.85	BNF 2014[50]
Sennoside B (as sennosides), 7.5 mg	60-tablet pack	Recipient	3.52	3.52	BNF 2014[50]
Sildenafil (as citrate), 25 mg	4-tablet pack	Recipient	1.09	1.09	BNF 2014[50]
Sodium chloride, 0.9%	20 × 2.5 ml spray	Recipient	20.60	20.60	BNF 2014[50]
Sodium chloride, 600 mg	100-tablet pack	Recipient	6.05	6.05	BNF 2014[50]
Sodium cromoglycate, 5 mg/dose	112-unit dose inhaler	Recipient	17.07	17.07	BNF 2014[50]
Sodium dihydrogen phosphate anhydrous, 1.936 g	100-tablet pack	Recipient	3.29	3.29	BNF 2014[50]
Sodium valproate, 200 mg	100-tablet pack	Recipient	4.49	4.49	BNF 2014[50]
Strepsils® (Reckitt Benckiser Group, Slough, UK)	24-lozenge pack	Recipient	2.99	2.99	Medical supplies
Sulfamethoxazole, 400 mg; and trimethoprim, 80 mg (co-trimoxazole)	28-tablet pack	Recipient	3.34	3.34	BNF 2014[50]
Tadalafil, 20 mg	8-tablet pack	Recipient	53.98	53.98	BNF 2014[50]
Tamsulosin hydrochloride, 400 µg	30-capsule pack	Recipient	4.62	4.62	BNF 2014[50]
T.E.D™ compression socks/hose (Medtronic, Minneapolis, MN, USA) (knee length)	Stocking	Recipient	8.12	8.12	Medical supplies
Teicoplanin	400-mg vial	Recipient	7.32	7.32	BNF 2014[50]
Theophylline [Uniphyllin® (Napp Pharmaceuticals Ltd, Cambridge, UK)], 200 mg	56-tablet pack	Recipient	2.96	2.96	BNF 2014[50]
Thiamine hydrochloride, 100 mg	100-tablet pack	Recipient	9.18	9.18	BNF 2014[50]
Tiotropium (as bromide), 18 µg	30-capsule pack	Recipient	34.87	34.87	BNF 2014[50]
Tobramycin, 60 mg/ml	56 × 5 ml – 300-mg unit	Recipient	1305.92	1305.92	BNF 2014[50]

TABLE 50 Unit costs of resources and interventions: detailed (*continued*)

Resource or intervention	Unit	Patient details	Standard donor lung transplantation (£)	EVLP transplantation (£)	Cost source
Tobramycin, 75 mg/ml	56 × 4-ml nebuliser	Recipient	1187.00	1187.00	BNF 2014[50]
Tramadol hydrochloride, 50 mg	30-capsule pack	Recipient	1.20	1.20	BNF 2014[50]
Tramadol hydrochloride, 50 mg	60-capsule pack	Recipient	6.56	6.56	BNF 2014[50]
Tramadol hydrochloride, 100 mg	60-capsule pack	Recipient	14.72	14.72	BNF 2014[50]
Ursodeoxycholic acid, 150 mg	60-tablet pack	Recipient	18.99	18.99	BNF 2014[50]
Ursodeoxycholic acid, 300 mg	60-tablet pack	Recipient	38.86	38.86	BNF 2014[50]
Valaciclovir (as hydrochloride), 500 mg	42-tablet pack	Recipient	8.50	8.50	BNF 2014[50]
Valganciclovir (as hydrochloride), 450 mg	60-tablet pack	Recipient	1081.46	1081.46	BNF 2014[50]
Vancomycin (as hydrochloride)	1-g vial	Recipient	12.99	12.99	BNF 2014[50]
Vitamin B compound strong	28-tablet pack	Recipient	1.95	1.95	BNF 2014[50]
Vitamins A, D, E	30-capsule pack	Recipient	5.93	5.93	BNF 2014[50]
Multivitamins	100-tablet pack	Recipient	9.21	9.21	BNF 2014[50]
Voriconazole, 200 mg	28-tablet pack	Recipient	1102.74	1102.74	BNF 2014[50]
Warfarin sodium, 3 mg	28-tablet pack	Recipient	1.07	1.07	BNF 2014[50]
Water for injections	5-ml ampoule	Recipient	0.24	0.24	BNF 2014[50]
Zopiclone, 3.75 mg	28-tablet pack	Recipient	1.68	1.68	BNF 2014[50]

EAC, equivalent annual cost; N_2, nitrogen gas; NHSBSA, NHS Business Service Authority; ODA, operating department assistant; VATS, video-assisted thoracoscopic surgery.

Appendix 7 NHS resource use

TABLE 51 NHS resource use: detailed table

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Donor's hospital					
Fixed costs					
Initial assessment					
ABG	Test	Donor	1.00	1.00	CRF p. 23/Anne Davison, NuTH, June 2015, personal communication
Bronchoscopy	Procedure	Donor	1.00	1.00	Paul Henderson, NuTH, September 2014, personal communication/ Katharine Thornalley, NuTH, June 2015, personal communication
Chest X-ray (radiography)	Test	Donor	1.00	1.00	CRF p. 23/Anne Davison, NuTH, June 2015, personal communication
ECG	Test	Donor	1.00	1.00	Anne Davison, NuTH, June 2015, personal communication
FBC	Test	Donor	1.00	1.00	Anne Davison, NuTH, June 2015, personal communication
Drugs					
Methylprednisolone (as sodium succinate)	500-mg vial	Donor	1.00	1.00	CRF p. 25
Methylprednisolone (as sodium succinate)	1-g vial	Donor	1.00	1.00	CRF p. 25/Tanveer Butt, NuTH, June 2015, personal communication
Methylprednisolone (as sodium succinate)	2-g vial	Donor	1.00	1.00	CRF p. 25
Lung retrieval					
Fixed costs					
Equipment					
DCD donor					
Bronchoscope	Instrument	Donor	1.00	1.00	Retrieval team/ Paul Henderson, NuTH, September 2014, personal communication
Pink spray 0.5% chlorhexidine	Spray	Donor	1.00	1.00	Retrieval team/ Paul Henderson, NuTH, September 2014, personal communication

continued

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
2 l of 0.9% sodium chloride solution	1-l solution	Donor	16.00	16.00	Retrieval team/ Paul Henderson, NuTH, September 2014, personal communication
Strapple tape	Roll	Donor	1.00	1.00	Retrieval team/ Paul Henderson, NuTH, September 2014, personal communication
DBD donor					
Blue 23-gauge 25-mm (1-inch) needles	1-inch needle	Donor	5.00	5.00	Retrieval team/ Paul Henderson, NuTH, September 2014, personal communication
Bronchoscope	Instrument	Donor	1.00	1.00	Retrieval team/ Paul Henderson, NuTH, September 2014, personal communication
1-l cardioplegia bag (green PLEGIVEX)	1-l bag	Donor	3.00	3.00	Retrieval team/ Paul Henderson, NuTH, September 2014, personal communication
Green vacutainers	Vacutainer	Donor	6.00	6.00	Retrieval team/ Paul Henderson, NuTH, September 2014, personal communication
i-STAT portable clinical analyser (Abbott Laboratories, Chicago, IL, USA)	Device	Donor	1.00	1.00	Retrieval team/ Paul Henderson, NuTH, September 2014, personal communication
i-STAT cartridges	Cartridge	Donor	8.00	8.00	Retrieval team/ Paul Henderson, NuTH, September 2014, personal communication
Pink spray 0.5% chlorhexidine	Spray	Donor	1.00	1.00	Retrieval team/ Paul Henderson, NuTH, September 2014, personal communication
1-l pressure infusion bag	1-l bag	Donor	1.00	1.00	Retrieval team/ Paul Henderson, NuTH, September 2014, personal communication
Red vacutainers	Vacutainer	Donor	6.00	6.00	Retrieval team/ Paul Henderson, NuTH, September 2014, personal communication
Sodium bicarbonate 8.4%	10-ml ampoule	Donor	1.00	1.00	Retrieval team/ Paul Henderson, NuTH, September 2014, personal communication
2 l of 0.9% sodium chloride solution	1-l solution	Donor	20.00	20.00	Retrieval team/ Paul Henderson, NuTH, September 2014, personal communication

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Spleen pots	Pot	Donor	6.00	6.00	Retrieval team/ Paul Henderson, NuTH, September 2014, personal communication
Strapple tape	Roll	Donor	1.00	1.00	Retrieval team/ Paul Henderson, NuTH, September 2014, personal communication
1-ml syringes	1-ml syringe	Donor	5.00	5.00	Retrieval team/ Paul Henderson, NuTH, September 2014, personal communication
Staff time					
Scout Team					
Retrieval surgeon (fellow)	Hour	Donor	0.80	0.80	Tanveer Butt, NuTH, June 2015, personal communication
Scrub nurse (band 5)	Hour	Donor	0.80	0.80	Tanveer Butt, NuTH, June 2015, personal communication
Retrieval team					
Perfusionist (band 7)	Hour	Donor	9.00	9.00	Tanveer Butt, NuTH, June 2015, personal communication/ Paul Henderson, NuTH, September 2014, personal communication
Retrieval surgeon (fellow)	Hour	Donor	9.00	9.00	Tanveer Butt, NuTH, June 2015, personal communication/ Paul Henderson, NuTH, September 2014, personal communication
Scrub nurse (band 5)	Hour	Donor	9.00	9.00	Tanveer Butt, NuTH, June 2015, personal communication/ Paul Henderson, NuTH, September 2014, personal communication
Tests					
Chest X-ray (radiography)	Test	Donor	1.00	1.00	CRF p. 23/Anne Davison, NuTH, June 2015, personal communication
Perfusion (dosage)					
2.8 l of PERFADEX solution	2.8-l solution	Donor	1.00	1.00	CRF p. 27/ Paul Henderson, NuTH, September 2014, personal communication/ Anders Andreasson, NuTH, September 2014, personal communication

continued

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
1 l of PERFADEX solution	1-l solution	Donor	1.00	1.00	CRF p. 27/ Paul Henderson, NuTH, September 2014, personal communication/ Anders Andreasson, NuTH, September 2014, personal communication
Calcium chloride 1 mmol/ml (1.7 ml/2.8 l PERFADEX and 0.6 ml/1 l PERFADEX)	10-ml ampoule	Donor	1.00	1.00	Paul Henderson, NuTH, September 2014, personal communication/ Anders Andreasson, NuTH, September 2014, personal communication
FLOLAN 0.5-mg vial (7 ml/2.8 l PERFADEX)	0.5-mg vial	Donor	3.00	3.00	Paul Henderson, NuTH, September 2014, personal communication/ Anders Andreasson, NuTH, September 2014, personal communication
FLOLAN 0.5-mg vial (2.5 ml/1 l PERFADEX)	0.5-mg vial	Donor	1.00	1.00	Paul Henderson, NuTH, September 2014, personal communication/ Anders Andreasson, NuTH, September 2014, personal communication
Heparin sodium 5000 units/5 ml (15,000 units/2.8 l PERFADEX)	5-ml ampoule	Donor	3.00	3.00	BNF 2014[50]
Heparin sodium 5000 units/5 ml (5000 units/1 l PERFADEX)	5-ml ampoule	Donor	1.00	1.00	BNF 2014[50]
THAM 1-ml ampoule (7 ml/2.8 l PERFADEX)	1-ml ampoule	Donor	7.00	7.00	Paul Henderson, NuTH, September 2014, personal communication/ Anders Andreasson, NuTH, September 2014, personal communication
THAM 1-ml ampoule (2.5 ml/1 l PERFADEX)	1-ml ampoule	Donor	3.00	3.00	Paul Henderson, NuTH, September 2014, personal communication/ Anders Andreasson, NuTH, September 2014, personal communication
Variable costs					
Travelling					
Scout team					
Road	Transport type/case	Donor	0.20	0.20	Brian Leadbitter, NuTH, June 2015, personal communication
Retrieval team					
Road	Transport type/case	Donor	0.74	0.74	Brian Leadbitter, NuTH, June 2015, personal communication

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Road and air	Transport type/case	Donor	0.26	0.26	Brian Leadbitter, NuTH, June 2015, personal communication
Organ (lung)					
Road	Transport type/case	Donor	0.50	0.50	Brian Leadbitter, NuTH, June 2015, personal communication
Road and air	Transport type/case	Donor	0.50	0.50	Brian Leadbitter, NuTH, June 2015, personal communication
Transplant preparation *Fixed costs*					
Contacting potential recipients					
Transplant co-ordinator	Hour	Recipient	1.00	1.00	Katie Morley, NuTH, October 2014, personal communication
Meeting potential recipients					
Transplant co-ordinator	Hour	Recipient	2.00	2.00	Katie Morley, NuTH, October 2014, personal communication
Tissue typing					
Tissue typing test	Test	Recipient	1.00	1.00	Katie Morley, NuTH, October 2014, personal communication
Tests					
ABG	Test	Recipient	1.00	1.00	CRF p. 20
Chest X-ray (radiography)	Test	Recipient	1.00	1.00	CRF p. 21
ECG	Test	Recipient	1.00	1.00	Katie Morley, NuTH, October 2014, personal communication/ Anne Davison, NuTH, June 2015, personal communication
FBC	Test	Recipient	1.00	1.00	CRF p. 20
Ward time					
Transplant centre ward	Bed-day	Recipient	1.00	1.00	Care Pathway/ Katie Morley, NuTH, October 2014, personal communication
Drugs					
Azathioprine 50 mg	56-tablet pack	Recipient	0.02	0.02	Andrew Fisher, NuTH, November 2015, personal communication

continued

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Variable costs					
Transfer to ward					
Air	Transport type	Recipient	Missing	Missing	Missing
Road	Transport type	Recipient	Missing	Missing	Missing
EVLP procedure *Fixed costs*					
Staff time					
Anaesthetic registrar	Hour	EVLP recipient	–	2.00	Katie Morley, NuTH, October 2014, personal communication/Paul Henderson, NuTH, September 2014, personal communication/ Anders Andreasson, NuTH, September 2014, personal communication
Consultant surgeon	Hour	EVLP recipient	–	0.33	Paul Henderson, NuTH, September 2014, personal communication
Perfusionist (band 7)	Hour	EVLP recipient	–	6.00	Anna Soderlund, Vivoline, July 2014, personal communication/ Anders Andreasson, NuTH, September 2014, personal communication
Scrub nurse/ODA (band 5)	Hour	EVLP recipient	–	3.00	Anna Soderlund, Vivoline, July 2014, personal communication/ Anders Andreasson, NuTH, September 2014, personal communication
Surgical fellow	Hour	EVLP recipient	–	4.00	Anna Soderlund, Vivoline, July 2014, personal communication/ Anders Andreasson, NuTH, September 2014, personal communication
Equipment					
Bronchoscope	Instrument	EVLP recipient	–	1.00	Anna Soderlund, Vivoline, July 2014, personal communication
DeBakey tissue forceps	Forceps	EVLP recipient	–	3.00	Anna Soderlund, Vivoline, July 2014, personal communication
McIndoe scissors	Scissor	EVLP recipient	–	1.00	Anna Soderlund, Vivoline, July 2014, personal communication
Nebuliser circuit	Item	EVLP recipient	–	1.00	Paul Henderson, NuTH, September 2014, personal communication

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
4–0 Prolene (no. 8935) suture pack	Pack	EVLP recipient	–	2.00	Anna Soderlund, Vivoline, July 2014, personal communication
10FG suction catheter (SHODS)	Catheter	EVLP recipient	–	1.00	Anna Soderlund, Vivoline, July 2014, personal communication
Suction connecting tubing	Tubing	EVLP recipient	–	1.00	Anna Soderlund, Vivoline, July 2014, personal communication
Consumables					
Nylon surgical tape	Roll	EVLP recipient	–	1.00	Anna Soderlund, Vivoline, July 2014, personal communication
Gas (2000 l of N_2/CO_2)	Cylinder	EVLP recipient	–	1.00	Anna Soderlund, Vivoline, July 2014, personal communication/ Anders Andreasson, NuTH, September 2014, personal communication
PERFADEX solution	1-l solution	EVLP recipient	–	2.00	Anna Soderlund, Vivoline, July 2014, personal communication
Packed red blood cells	274-ml bag	EVLP recipient	–	2.00	Anna Soderlund, Vivoline, July 2014, personal communication/ Anders Andreasson, NuTH, September 2014, personal communication
Syringes for blood gases	Syringe	EVLP recipient	–	9.00	Anna Soderlund, Vivoline, July 2014, personal communication
Syringes (other)	Syringe	EVLP recipient	–	10.00	Anna Soderlund, Vivoline, July 2014, personal communication
Vivoline disposable lung set	Set	EVLP recipient	–	1.00	Anna Soderlund, Vivoline, July 2014, personal communication
Miscellaneous equipment					
Blood gases samples	Sample	EVLP recipient	–	20.00	Anna Soderlund, Vivoline, July 2014, personal communication
Vivoline system	System	EVLP recipient	–	1.00	Anna Soderlund, Vivoline, July 2014, personal communication/ protocol[103]
Theatre usage					
Operating theatre	Hour	EVLP recipient	–	6.00	Protocol p. 35/ Anders Andreasson, NuTH, September 2014, personal communication

continued

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Drugs					
2 l of Steen Solution	500-ml solution	EVLP recipient	–	4.00	CRF p. 34/ Anders Andreasson, NuTH, September 2014, personal communication
Heparin sodium, 1000 units/ml	1-ml ampoule	EVLP recipient	–	1.00	CRF p. 34/ Anders Andreasson, NuTH, September 2014, personal communication
Heparin sodium, 5000 units/ml	1-ml ampoule	EVLP recipient	–	2.00	CRF p. 34/ Anders Andreasson, NuTH, September 2014, personal communication
Insulin human (ACTRAPID HM), 100 IU/ml	10-ml vial	EVLP recipient	–	1.00	CRF p. 34/ Anders Andreasson, NuTH, September 2014, personal communication
Methylprednisolone (as sodium succinate)	500-mg vial	EVLP recipient	–	1.00	CRF p. 34/ Anders Andreasson, NuTH, September 2014, personal communication
Methylprednisolone (as sodium succinate)	1-g vial	EVLP recipient	–	1.00	CRF p. 34/ Anders Andreasson, NuTH, September 2014, personal communication
Methylprednisolone (as sodium succinate)	2-g vial	EVLP recipient	–	1.00	CRF p. 34/ Anders Andreasson, NuTH, September 2014, personal communication
THAM, 30 mg/ml (3.0 mmol/ml)	1-ml ampoule	EVLP recipient	–	20.00	CRF p. 34/ Anders Andreasson, NuTH, September 2014, personal communication
Antibiotics					
Meropenem (as trihydrate)	500-mg vial	EVLP recipient	–	2.00	CRF p. 34/ Anders Andreasson, NuTH, September 2014, personal communication/ Andrew Fisher, NuTH, November 2015, personal communication
Moxifloxacin (as hydrochloride), 1.6 mg/ml	250-ml solution for infusion bottle (400 mg)	EVLP recipient	–	1.00	CRF p. 34/ Anders Andreasson, NuTH, September 2014, personal communication/ Andrew Fisher, NuTH, November 2015, personal communication

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Antifungal					
Amphotericin B	50-mg vial	EVLP recipient	–	1.00	CRF p. 34/ Anders Andreasson, NuTH, September 2014, personal communication/ Andrew Fisher, NuTH, November 2015, personal communication
Lung transplant *Fixed costs*					
Anaesthetic preparation					
Anaesthetic room	Hour	Recipient	0.75	0.75	Transplant co-ordinators
Anaesthetic nurse (band 5)	Hour	Recipient	0.75	0.75	Transplant co-ordinators
Consultant anaesthetist	Hour	Recipient	0.75	0.75	Transplant co-ordinators
Staff time					
Single lung surgery					
Anaesthetic fellow	Hour	Recipient	4.00	4.00	Qualtrics survey/ Paul Henderson, NuTH, September 2014, personal communication
Anaesthetic nurse (band 5)	Hour	Recipient	4.00	4.00	Qualtrics survey/ Paul Henderson, NuTH, September 2014, personal communication
Consultant anaesthetist	Hour	Recipient	4.00	4.00	Qualtrics survey/ Paul Henderson, NuTH, September 2014, personal communication
Consultant surgeon	Hour	Recipient	4.00	4.00	Qualtrics survey/ Paul Henderson, NuTH, September 2014, personal communication
Perfusionist (band 7)	Hour	Recipient	4.00	4.00	Qualtrics survey/ Paul Henderson, NuTH, September 2014, personal communication
Scrub nurse (band 7)	Hour	Recipient	4.00	4.00	Qualtrics survey/ Paul Henderson, NuTH, September 2014, personal communication
Scrub nurse (band 5)	Hour	Recipient	4.00	4.00	Qualtrics survey/ Paul Henderson, NuTH, September 2014, personal communication
Surgical fellow	Hour	Recipient	4.00	4.00	Qualtrics survey/ 0Paul Henderson, NuTH, September 2014, personal communication

continued

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Double lung surgery					
Anaesthetic fellow	Hour	Recipient	7.00	7.00	Qualtrics survey/ Paul Henderson, NuTH, September 2014, personal communication
Anaesthetic nurse (band 5)	Hour	Recipient	7.00	7.00	Qualtrics survey/ Paul Henderson, NuTH, September 2014, personal communication
Consultant anaesthetist	Hour	Recipient	7.00	7.00	Qualtrics survey/ Paul Henderson, NuTH, September 2014, personal communication
Consultant surgeon	Hour	Recipient	7.00	7.00	Qualtrics survey/ Paul Henderson, NuTH, September 2014, personal communication
Perfusionist (band 7)	Hour	Recipient	7.00	7.00	Qualtrics survey/ Paul Henderson, NuTH, September 2014, personal communication
Scrub nurse (band 7)	Hour	Recipient	7.00	7.00	Qualtrics survey/ Paul Henderson, NuTH, September 2014, personal communication
Scrub nurse (band 5)	Hour	Recipient	7.00	7.00	Qualtrics survey/ Paul Henderson, NuTH, September 2014, personal communication
Surgical fellow	Hour	Recipient	7.00	7.00	Qualtrics survey/ Paul Henderson, NuTH, September 2014, personal communication
Theatre usage					
Single lung surgery					
Operating theatre	Hour	Recipient	4.00	4.00	CRF p. 43/Qualtrics survey
Double lung surgery					
Operating theatre	Hour	Recipient	7.00	7.00	CRF p. 43/Qualtrics survey
Equipment/consumables					
Usual surgical set	Set	Recipient	Missing	Missing	Missing
Post-operative care *Fixed costs*					
Staff time in ITU/HDU					
Anaesthetic fellow	Hour	Recipient	1.50	1.50	Qualtrics survey/ Andrew Fisher, NuTH, November 2015, personal communication

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Consultant anaesthetist	Hour	Recipient	0.50	0.50	Qualtrics survey/ Andrew Fisher, NuTH, November 2015, personal communication
Consultant physician	Hour	Recipient	0.17	0.17	Qualtrics survey/ Andrew Fisher, NuTH, November 2015, personal communication
Consultant surgeon	Hour	Recipient	0.25	0.25	Qualtrics survey/ Andrew Fisher, NuTH, November 2015, personal communication
Surgical fellow	Hour	Recipient	0.25	0.25	Qualtrics survey/ Andrew Fisher, NuTH, November 2015, personal communication
Staff time in hospital					
Consultant physician	Hour	Recipient	0.34	0.34	Andrew Fisher, NuTH, November 2015, personal communication
Surgical fellow	Hour	Recipient	0.25	0.25	Andrew Fisher, NuTH, November 2015, personal communication
Transplant specialist registrar	Hour	Recipient	0.67	0.67	Andrew Fisher, NuTH, November 2015, personal communication
Tests					
ABG	Test	Recipient	1.00	1.00	CRF p. 47
Chest X-ray (radiography)	Test	Recipient	1.00	1.00	CRF p. 56
FBC	Test	Recipient	1.00	1.00	CRF p. 56
Pulmonary/lung function test	Test	Recipient	1.00	1.00	CRF p. 56
Variable costs					
***Ward usage* (if needed)**					
HDU care	Bed-day	Recipient	10.00	10.00	CRF p. 51/52
ITU care	Bed-day	Recipient	11.00	11.00	CRF p. 51/52
ITU/HDU readmission	Bed-day	Recipient	15.00	15.00	CRF p. 52
Level 1 ward care (hospital stay)	Bed-day	Recipient	34.00	34.00	Andrew Fisher, NuTH, November 2015, personal communication/ CRF p. 51/52
***Procedures* (if needed)**					
Bronchoscopy	Procedure	Recipient	1.00	1.00	CRF p. 46
Tracheostomy	Procedure	Recipient	1.00	1.00	CRF p. 51

continued

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Equipment **(if needed)**					
ECMO	Machine	Recipient	1.00	1.00	CRF p. 45
iLA membrane ventilator	Device	Recipient	1.00	1.00	CRF p. 45
Consumables **(if needed)**					
2 l of colloid (plasma and plasma substitutes)	500 ml	Recipient	4.00	4.00	CRF p. 45
1 l of crystalloid (fluids containing electrolytes)	500 ml	Recipient	2.00	2.00	CRF p. 45
Fresh-frozen plasma	271-ml bag	Recipient	3.00	3.00	CRF p. 45
Packed red blood cells	274-ml bag	Recipient	4.00	4.00	CRF p. 45
Platelets	250-ml bag	Recipient	2.00	2.00	CRF p. 45
Inotropes **(if needed)**					
Adrenaline (base), 1 mg/10 ml (1 in 10,000)	10-ml pre-filled disposable injection	Recipient	1.00	1.00	CRF p. 45
Dobutamine (as hydrochloride), 12.5 mg/ml	20-ml ampoule	Recipient	1.00	1.00	CRF p. 45
Glyceryl trinitrate, 1 mg/ml	50-ml vial	Recipient	1.00	1.00	CRF p. 45
Milrinone, 1 mg/ml	10-ml ampoule	Recipient	1.00	1.00	CRF p. 45
Noradrenaline (as acid tartrate), 1 mg/ml	4-ml ampoule	Recipient	1.00	1.00	CRF p. 45
Pitressin (argipressin – synthetic vasopressin), 20 units/ml	1-ml ampoule	Recipient	1.00	1.00	CRF p. 45
Other					
Dopamine hydrochloride, 40 mg/ml	5-ml ampoule	Recipient	1.00	1.00	CRF p. 46
Enoximone, 5 mg/ml	20-ml ampoule	Recipient	1.00	1.00	CRF p. 46
Isoprenaline	–	Recipient	1.00	1.00	CRF p. 46
Metaraminol	–	Recipient	1.00	1.00	CRF p. 46
Post implantation haemodynamic support **(if needed)**					
Adrenaline (base), 1 mg/10 ml (1 in 10,000)	10-ml pre-filled disposable injection	Recipient	1.00	1.00	CRF p. 50
Dobutamine (as hydrochloride), 12.5 mg/ml	20-ml ampoule	Recipient	1.00	1.00	CRF p. 50
Glyceryl trinitrate, 1 mg/ml	50-ml vial	Recipient	1.00	1.00	CRF p. 50
Milrinone, 1 mg/ml	10-ml ampoule	Recipient	1.00	1.00	CRF p. 50
Noradrenaline (as acid tartrate), 1 mg/ml	4-ml ampoule	Recipient	1.00	1.00	CRF p. 50
Pitressin (argipressin – synthetic vasopressin), 20 units/ml	1-ml ampoule	Recipient	1.00	1.00	CRF p. 50

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Complications **(if reported)**					
Cerebrovascular accident	Treatment	Recipient	1.00	1.00	CRF p. 52
Hemofiltration	Procedure	Recipient	14.00	14.00	CRF p. 52
Haemodialysis	Procedure (days)	Recipient	9.00	9.00	CRF p. 52
Re-exploration	Procedure	Recipient	1.00	1.00	CRF p. 52
Airway complications **(if reported)**					
Balloon dilatation	Procedure	Recipient	1.00	1.00	CRF p. 53
Cryotherapy	Procedure	Recipient	1.00	1.00	CRF p. 53
Diathermy	Procedure	Recipient	1.00	1.00	CRF p. 53
Stenting	Procedure	Recipient	1.00	1.00	CRF p. 53
Surgical intervention	Procedure	Recipient	1.00	1.00	CRF p. 53
ITU rejection episodes **(if reported)**					
Ward usage					
HDU care	Bed-day	Recipient	18.00	18.00	CRF p. 58
ITU care	Bed-day	Recipient	26.00	26.00	CRF p. 58
Procedures					
Clinical diagnosis/biopsy	Procedure	Recipient	1.00	1.00	CRF p. 57
Treatment					
Cefuroxime (as sodium), 750 mg	750-mg vial	Recipient	1.00	1.00	CRF p. 54
Methylprednisolone (as sodium succinate)	1-g vial	Recipient	1.00	1.00	CRF p. 54
Piperacillin (as sodium), 2 g; and tazobactam (as sodium), 250 mg (Tazocin)	2.25-g vial	Recipient	1.00	1.00	CRF p. 54
Changes in maintenance therapy					
Methylprednisolone, 100 mg	20-tablet pack	Recipient	0.50	0.50	CRF p. 54
Tacrolimus, 5 mg/ml	1-ml ampoule	Recipient	1.00	1.00	CRF p. 54
Ward rejection episodes **(if reported)**					
Procedures					
Clinical diagnosis/biopsy	Procedure	Recipient	1.00	1.00	CRF p. 57
Treatment					
Methylprednisolone (as sodium succinate), 500 mg	500-mg vial	Recipient	1.00	1.00	CRF p. 57
Methylprednisolone (as sodium succinate)	1-g vial	Recipient	1.00	1.00	CRF p. 57
Methylprednisolone, 100 mg	20-tablet pack	Recipient	1.00	1.00	CRF p. 57

continued

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Prednisolone acetate, 25 mg/ml	1-ml ampoule	Recipient	1.00	1.00	CRF p. 57
Prednisolone, 25 mg	56-tablet pack	Recipient	1.00	1.00	CRF p. 57
Sulfamethoxazole, 400 mg; and trimethoprim, 80 mg (co-trimoxazole 480 mg)	28-tablet pack	Recipient	1.00	1.00	CRF p. 57
Tacrolimus, 5 mg/ml	1-ml ampoule	Recipient	1.00	1.00	CRF p. 57
***Infection episodes* (if reported)**					
Treatment					
Aciclovir (as sodium), 25 mg/ml	20-ml vial (500 mg)	Recipient	15.00	15.00	CRF p. 58
Adefovir dipivoxil, 10 mg	30-tablet pack	Recipient	1.00	1.00	CRF p. 58
Amikacin (as sulfate), 250 mg/ml	2-ml vial	Recipient	30.00	30.00	CRF p. 58
Amoxicillin (as trihydrate), 500 mg	21-capsule pack	Recipient	1.00	1.00	CRF p. 58
Amoxicillin (as trihydrate), 500 mg; and clavulanic acid (as potassium), 125 mg (co-amoxiclav)	21-tablet pack	Recipient	1.00	1.00	CRF p. 58
Amphotericin B liposomal (AmBisome)	50-mg vial	Recipient	7.00	7.00	CRF p. 58
Amphotericin B (as sodium deoxycholate complex)	50-mg vial	Recipient	14.00	14.00	CRF p. 58
Anidulafungin	100-mg vial	Recipient	16.00	16.00	CRF p. 58
Azithromycin (as dihydrate), 250 mg	4-capsule pack	Recipient	1.00	1.00	CRF p. 58
Aztreonam	1-g vial	Recipient	42.00	42.00	CRF p. 58
BAL	Procedure	Recipient	1.00	1.00	CRF p. 58
Budesonide, 100 µg; and formoterol fumarate, 6 µg (Symbicort Turbohaler)	120-dose inhaler	Recipient	1.00	1.00	CRF p. 58
Caspofungin (as acetate)	70-mg vial	Recipient	14.00	14.00	CRF p. 58
Ceftazidime (as pentahydrate)	2-g vial	Recipient	42.00	42.00	CRF p. 58
Cefuroxime (as sodium)	750-mg vial	Recipient	21.00	21.00	CRF p. 58
Chloramphenicol (as sodium succinate)	1-g vial	Recipient	84.00	84.00	CRF p. 58
Ciprofloxacin (as lactate), 2 mg/ml	200-ml solution for infusion bottle	Recipient	14.00	14.00	CRF p. 58
Ciprofloxacin (as hydrochloride), 500 mg	20-tablet pack	Recipient	1.00	1.00	CRF p. 58

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Ciprofloxacin (as hydrochloride), 3 mg/ml	5-ml 0.3% eye drops	Recipient	2.00	2.00	CRF p. 58
Clarithromycin	500-mg vial	Recipient	10.00	10.00	CRF p. 58
Clindamycin (as phosphate), 150 mg/ml	4-ml ampoule	Recipient	20.00	20.00	CRF p. 58
Colistimethate sodium	2-million-unit vial	Recipient	28.00	28.00	CRF p. 58
Domperidone (as maleate), 10 mg	100-tablet pack	Recipient	1.00	1.00	CRF p. 58
Doxycycline (as hyclate), 100 mg	8-capsule pack	Recipient	1.00	1.00	CRF p. 58
Eradication therapy for *H. pylori*	7-day course	Recipient	1.00	1.00	CRF p. 58
Ertapenem (as sodium)	1-g vial	Recipient	14.00	14.00	CRF p. 58
Ethambutol hydrochloride, 100 mg	56-tablet pack	Recipient	1.00	1.00	CRF p. 58
Flucloxacillin (as sodium)	28-capsule pack	Recipient	1.00	1.00	CRF p. 58
Flucloxacillin (as sodium)	1-g vial	Recipient	12.00	12.00	CRF p. 58
Fluconazole, 50 mg	7-capsule pack	Recipient	8.00	8.00	CRF p. 58
Fluconazole, 2 mg/ml	100-ml solution for infusion bottle	Recipient	43.00	43.00	CRF p. 58
Fluconazole, 50 mg	7-capsule pack	Recipient	8.00	8.00	CRF p. 58
Foscarnet sodium, 24 mg/ml	250-ml solution for infusion bottle	Recipient	42.00	42.00	CRF p. 58
Fosfomycin (as sodium)	2-g vial	Recipient	30.00	30.00	CRF p. 58
Furosemide, 10 mg/ml	5-ml ampoule	Recipient	21.00	21.00	CRF p. 58
Ganciclovir (as sodium)	500-mg vial	Recipient	42.00	42.00	CRF p. 58
Gentamycin (as sulfate), 40 mg/ml	2-ml vial	Recipient	28.00	28.00	CRF p. 58
Immunoglobulin	10-g vial	Recipient	1.00	1.00	CRF p. 58
Itraconazole, 10 mg/ml	25-ml ampoule	Recipient	16.00	16.00	CRF p. 58
Lamivudine, 150 mg	60-tablet pack	Recipient	1.00	1.00	CRF p. 58
Lesion excision	Day case	Recipient	1.00	1.00	CRF p. 58
Linezolid, 2 mg/ml	300-ml infusion bag	Recipient	84.00	84.00	CRF p. 58
Meropenem (as trihydrate)	1-g vial	Recipient	12.25	12.25	CRF p. 58
Methylprednisolone (as sodium succinate)	1-g vial	Recipient	3.00	3.00	CRF p. 58
Metochlopramide hydrochloride, 5 mg/ml	2-ml ampoule	Recipient	15.00	15.00	CRF p. 58

continued

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Metronidazole, 200 mg	21-tablet pack	Recipient	2.00	2.00	CRF p. 58
Micafungin (as sodium)	100-mg vial	Recipient	14.00	14.00	CRF p. 58
Moxifloxacin (as hydrochloride), 1.6 mg/ml	250-ml solution for infusion bottle	Recipient	14.00	14.00	CRF p. 58
Oseltamivir (as phosphate), 75 mg	10-capsule pack	Recipient	1.00	1.00	CRF p. 58
Packed red blood cells	274-ml bag	Recipient	1.00	1.00	CRF p. 58
Piperacillin (as sodium), 4 g; and tazobactam (as sodium), 500 mg (Tazocin)	4.5-g vial	Recipient	43.00	43.00	CRF p. 58
Posaconazole, 100 mg	96-tablet pack	Recipient	1.00	1.00	CRF p. 58
Prednisolone, 25 mg	56-tablet pack	Recipient	1.00	1.00	CRF p. 58
Respiratory failure (inpatient)	Treatment	Recipient	1.00	1.00	CRF p. 58
Sirolimus, 2 mg	30-tablet pack	Recipient	1.00	1.00	CRF p. 58
Streptokinase	250,000-unit powder vial	Recipient	12.00	12.00	CRF p. 58
Sulfamethoxazole, 80 mg; and trimethoprim, 16 mg (Septrin)	5-ml ampoule	Recipient	24.00	24.00	CRF p. 58
Surgical intervention or VATS	Procedure	Recipient	1.00	1.00	CRF p. 58
Teicoplanin	200-mg vial	Recipient	10.00	10.00	CRF p. 58
Trimethoprim, 100 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 58
Tobramycin (as sulfate), 40 mg/ml	1-ml vial	Recipient	12.25	12.25	CRF p. 58
Tigecycline	50-mg vial	Recipient	30.00	30.00	CRF p. 58
Valganciclovir (as hydrochloride), 450 mg	60-tablet pack	Recipient	1.00	1.00	CRF p. 58
Vancomycin (as hydrochloride)	1-g vial	Recipient	14.00	14.00	CRF p. 58
Voriconazole	200-mg vial	Recipient	34.00	34.00	CRF p. 58
Ward usage					
HDU care	Bed-day	Recipient	18.00	18.00	CRF p. 58
ITU care	Bed-day	Recipient	26.00	26.00	CRF p. 58
Outpatient care *Fixed costs*					
Outpatient reviews					
Bronchoscopy	Procedure/visit (4 visits)	Recipient	1.00	1.00	CRF
Chest X-ray (radiography)	Test/visit (4 visits)	Recipient	1.00	1.00	CRF
FBC	Test/visit (4 visits)	Recipient	1.00	1.00	CRF

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Liver function test	Test/visit (4 visits)	Recipient	1.00	1.00	Andrew Fisher, NuTH, November 2015, personal communication
Pulmonary/lung function test	Test/visit (4 visits)	Recipient	1.00	1.00	CRF
Urea and electrolytes test	Test/visit (4 visits)	Recipient	1.00	1.00	Andrew Fisher, NuTH, November 2015, personal communication
Staff time					
Consultant physician	Hour/visit (4 visits)	Recipient	0.50	0.50	Care pathway/ Katie Morley, NuTH, October 2014, personal communication
Scrub nurse (band 5)	Hour/visit (4 visits)	Recipient	0.50	0.50	Care pathway/Katie Morley, NuTH, October 2014, personal communication
Variable costs					
***Rejection episodes* (if reported)**					
Procedures					
Clinical diagnosis/biopsy	Procedure	Recipient	1.00	1.00	CRF
Ventilation–perfusion scan	Test	Recipient	1.00	1.00	CRF
Treatment					
Anti-thymocyte immunoglobulin (rabbit), 25 mg	25-mg vial	Recipient	40.00	40.00	CRF
Azathioprine, 25 mg	28-tablet pack	Recipient	1.00	1.00	CRF
Azathioprine, 50 mg	56-tablet pack	Recipient	2.00	2.00	CRF
Ciclosporin, 25 mg	30-capsule pack	Recipient	1.00	1.00	CRF
Ciclosporin, 50 mg	30-capsule pack	Recipient	1.00	1.00	CRF
Ciclosporin, 100 mg	30-capsule pack	Recipient	3.00	3.00	CRF
Ciclosporin (NEORAL), 10 mg	60-capsule pack	Recipient	1.00	1.00	CRF
Ciclosporin (NEORAL), 25 mg	30-capsule pack	Recipient	1.00	1.00	CRF
Ciclosporin (NEORAL), 50 mg	30-capsule pack	Recipient	1.00	1.00	CRF
Ciclosporin (NEORAL), 100 mg	30-capsule pack	Recipient	1.00	1.00	CRF
Immunoglobulin	10-g vial	Recipient	1.00	1.00	CRF
Meropenem (as trihydrate)	1-g vial	Recipient	30.00	30.00	CRF
Methylprednisolone (as sodium succinate)	125-mg vial	Recipient	4.00	4.00	CRF

continued

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Methylprednisolone (as sodium succinate)	500-mg vial	Recipient	3.00	3.00	CRF
Methylprednisolone (as sodium succinate)	1-g vial	Recipient	3.00	3.00	CRF
Mycophenolate mofetil, 500 mg	50-tablet pack	Recipient	1.00	1.00	CRF
Mycophenolate mofetil, 250 mg	100-capsule pack	Recipient	1.00	1.00	CRF
Prednisolone, 1 mg	28-tablet pack	Recipient	1.00	1.00	CRF
Prednisolone, 5 mg	28-tablet pack	Recipient	2.00	2.00	CRF
Prednisolone, 25 mg	56-tablet pack	Recipient	1.00	1.00	CRF
Rituximab, 100 mg/ml	10-ml vial	Recipient	4.00	4.00	CRF
Tacrolimus (Prograf), 500 µg	50-capsule pack	Recipient	1.00	1.00	CRF
Tacrolimus (Prograf), 1 mg	50-capsule pack	Recipient	4.00	4.00	CRF
Tacrolimus (Prograf), 1 mg	100-capsule pack	Recipient	1.00	1.00	CRF
Tacrolimus (Prograf), 5 mg	50-capsule pack	Recipient	1.00	1.00	CRF
Valganciclovir (as hydrochloride), 450 mg	60-tablet pack	Recipient	1.00	1.00	CRF
Ward usage					
HDU care	Bed-day	Recipient	30.00	30.00	CRF
ITU care	Bed-day	Recipient	7.00	7.00	CRF
***GP visits* (if needed)**					
Out-of-surgery visit	Visit	Recipient	1.00	1.00	CRF
Surgery visit	Visit	Recipient	1.00	1.00	CRF
Transplant centre advice	Call	Recipient	1.00	1.00	CRF
***Unplanned hospital admission* (if needed)**					
Treatment					
Aciclovir (as sodium), 25 mg/ml	20-ml vial	Recipient	15.00	15.00	CRF
Aciclovir, 400 mg	56-tablet pack	Recipient	1.00	1.00	CRF
Adrenaline (base), 100 µg/ml (1 in 10,000)	10-ml pre-filled disposable injection	Recipient	1.00	1.00	CRF
Amiodarone hydrochloride, 30 mg/ml	10-ml pre-filled disposable injection	Recipient	7.00	7.00	CRF
Amoxicillin (as sodium), 500 mg; and clavulanic acid (as potassium), 125 mg (co-amoxiclav)	500/100-mg vial	Recipient	15.00	15.00	CRF
Amphotericin B	50-mg vial	Recipient	14.00	14.00	CRF

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Aspirin, 300 mg	32-tablet pack	Recipient	1.00	1.00	CRF
Azathioprine, 25 mg	28-tablet pack	Recipient	1.00	1.00	CRF
Azithromycin (as dihydrate), 250 mg	4-capsule pack	Recipient	1.00	1.00	CRF
Aztreonam	1-g vial	Recipient	42.00	42.00	CRF
Balloon dilatation	Procedure	Recipient	1.00	1.00	CRF
Basiliximab	20-mg vial	Recipient	2.00	2.00	CRF
Bisoprolol fumarate, 10 mg	28-tablet pack	Recipient	1.00	1.00	CRF
Bortezomib	3.5-mg vial	Recipient	1.00	1.00	CRF
Bronchoscopy	Procedure	Recipient	1.00	1.00	CRF
Budesonide, 100 µg; and formoterol fumarate dihydrate, 6 µg (Symbicort 100/6 Turbohaler®)	120-dose unit inhaler	Recipient	1.00	1.00	CRF
Calcium gluconate, 1 g	28-tablet pack	Recipient	1.00	1.00	CRF
Calcium polystyrene sulfonate (Calcium Resonium)	300-g powder	Recipient	1.00	1.00	CRF
Candesartan cilexetil, 4 mg	28-tablet pack	Recipient	2.00	2.00	CRF
Caspofungin (as acetate)	70-mg vial	Recipient	14.00	14.00	CRF
Ciclosporin, 100 mg	30-capsule pack	Recipient	2.00	2.00	CRF
Ciclosporin, 50 mg/ml	5-ml ampoule	Recipient	17.00	17.00	CRF
Ciprofloxacin (as hydrochloride), 500 mg	20-tablet pack	Recipient	2.00	2.00	CRF
Clarithromycin	500-mg vial	Recipient	10.00	10.00	CRF
Clinical diagnosis/biopsy	Procedure	Recipient	1.00	1.00	CRF
Colistimethate sodium	1-million-unit vial	Recipient	28.00	28.00	CRF
Colistimethate sodium	2-million-unit vial	Recipient	28.00	28.00	CRF
Computerised tomography	Procedure	Recipient	1.00	1.00	CRF
DeBakey tissue forceps	Forceps	Recipient	1.00	1.00	CRF
Docusate sodium, 100 mg	30-capsule pack	Recipient	4.00	4.00	CRF
Doxazosin (as mesilate), 4 mg	28-tablet pack	Recipient	2.00	2.00	CRF
Doxycycline (as hyclate), 100 mg	8-capsule pack	Recipient	1.00	1.00	CRF
ECG	24-hour test	Recipient	24.00	24.00	CRF
Enoxaparin sodium (Clexane Forte), 150 mg	1-ml pre-filled disposable injection	Recipient	5.00	5.00	CRF
ECMO	Machine	Recipient	1.00	1.00	CRF

continued

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Filgrastim, 30 million units (300 µg/ml)	1-ml vial	Recipient	14.00	14.00	CRF
Flucloxacillin (as sodium)	1-g vial	Recipient	12.00	12.00	CRF
Fluticasone propionate, 250 µg; and salmeterol xinafoate, 50 µg (Seretide 250 Accuhaler)	120-unit dose inhaler	Recipient	1.00	1.00	CRF
Foscarnet sodium, 24 mg/ml	250-ml solution for infusion bottle	Recipient	1.00	1.00	CRF
Furosemide, 10 mg/ml	5-ml ampoule	Recipient	21.00	21.00	CRF
Ganciclovir (as sodium)	500-mg vial	Recipient	42.00	42.00	CRF
Gastrografin	Solution	Recipient	1.00	1.00	CRF
Glucose anhydrous, 50 mg/ml	1000-ml bag	Recipient	7.00	7.00	CRF
iLA membrane ventilator	Device	Recipient	1.00	1.00	CRF
Immunoglobulin	10-g vial	Recipient	1.00	1.00	CRF
Insulin, 3 ml	5 × 3-ml pre-filled disposable injection devices	Recipient	1.00	1.00	CRF
Intubation	Procedure	Recipient	1.00	1.00	CRF
Hydralazine hydrochloride, 50 mg	56-tablet pack	Recipient	1.00	1.00	CRF
Hydrocortisone (as sodium succinate)	100-mg vial	Recipient	28.00	28.00	CRF
Lansoprazole, 30 mg	28-capsule pack	Recipient	1.00	1.00	CRF
Level 1 ward care (hospital stay)	Bed-day	Recipient	1.00	1.00	CRF
Macrogol compound oral powder	50-sachet pack	Recipient	1.00	1.00	CRF
Magnesium hydroxide with liquid paraffin	150-ml bottle	Recipient	1.00	1.00	CRF
Magnesium sulfate heptahydrate, 100 mg	10-ml ampoule	Recipient	1.00	1.00	CRF
Magnetic resonance imaging scan	Test	Recipient	1.00	1.00	CRF
Meropenem (as trihydrate)	1-g vial	Recipient	11.00	11.00	CRF
Methylprednisolone (as sodium succinate), 500 mg	500-mg vial	Recipient	3.00	3.00	CRF
Methylprednisolone (as sodium succinate)	1-g vial	Recipient	3.00	3.00	CRF
Metoclopramide hydrochloride, 5 mg/ml	2-ml ampoule	Recipient	4.00	4.00	CRF
Midazolam (as hydrochloride), 1 mg/ml	5-ml ampoule	Recipient	1.00	1.00	CRF

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Minocycline (as hydrochloride), 100 mg	28-tablet pack	Recipient	1.00	1.00	CRF
Moxifloxacin (as hydrochloride), 1.6 mg/ml	250-ml solution for infusion bottle	Recipient	14.00	14.00	CRF
Nefopam hydrochloride, 30 mg	90-tablet pack	Recipient	1.00	1.00	CRF
Non-invasive ventilation	Procedure	Recipient	1.00	1.00	CRF
Normal immunoglobulin, 10 g	200-ml solution for infusion bottle	Recipient	1.00	1.00	CRF
Oxycodone hydrochloride, 10 mg/ml	120-ml oral solution	Recipient	1.00	1.00	CRF
Packed red blood cells	274-ml bag	Recipient	2.00	2.00	CRF
Phosphate enema	133-ml enema pack	Recipient	1.00	1.00	CRF
Piperacillin (as sodium), 4 g; and tazobactam (as sodium), 500 mg (Tazocin)	4.5-g vial	Recipient	40.00	40.00	CRF
Posaconazole, 100 mg	96-tablet pack	Recipient	1.00	1.00	CRF
Prednisolone, 5 mg	28-tablet pack	Recipient	4.00	4.00	CRF
Pregabalin, 150 mg	56-capsule pack	Recipient	1.00	1.00	CRF
Redo lung transplantation	Procedure	Recipient	1.00	1.00	CRF
Renal support	Treatment	Recipient	1.00	1.00	CRF
Ribavirin, 200 mg	42-tablet pack	Recipient	1.00	1.00	CRF
Ribavirin, 400 mg	56-tablet pack	Recipient	1.00	1.00	CRF
Salbutamol (as sulfate), 5 mg/2.5 ml	20-unit dose nebuliser liquid vial	Recipient	1.00	1.00	CRF
Sirolimus, 2 mg	30-tablet pack	Recipient	2.00	2.00	CRF
Sodium bicarbonate, 42 mg/ml	500-ml intravenous infusion bottle	Recipient	1.00	1.00	CRF
2 l of 0.9% sodium chloride solution	1-l solution	Recipient	20.00	20.00	CRF
Stenting	Procedure	Recipient	1.00	1.00	CRF
Sulfamethoxazole, 80 mg; and trimethoprim, 16 mg (Septrin)	5-ml ampoule	Recipient	18.00	18.00	CRF
Sulfamethoxazole, 400 mg; and trimethoprim, 80 mg (co-trimoxazole)	5-ml ampoule	Recipient	12.00	12.00	CRF
Surgical intervention	Procedure	Recipient	1.00	1.00	CRF

continued

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Tacrolimus (Prograf), 1 mg	50-capsule pack	Recipient	4.00	4.00	CRF
Tacrolimus (Prograf), 1 mg	100-capsule pack	Recipient	1.00	1.00	CRF
Tacrolimus (Prograf), 5 mg/ml	10 × 1-ml ampoules	Recipient	7.00	7.00	CRF
Tinzaparin sodium, 20,000 units/ml (Innohep)	0.5-ml vial	Recipient	630.00	630.00	CRF
Tracheostomy	Procedure	Recipient	1.00	1.00	CRF
Tramadol hydrochloride, 150 mg	60-capsule pack	Recipient	1.00	1.00	CRF
Ultrasound scan	Test	Recipient	1.00	1.00	CRF
Valganciclovir (as hydrochloride), 450 mg	60-tablet pack	Recipient	1.00	1.00	CRF
Vancomycin (as hydrochloride), 125 mg	28-capsule pack	Recipient	2.00	2.00	CRF
Voriconazole	200-mg vial	Recipient	78.00	78.00	CRF
Warfarin sodium, 3 mg	28-tablet pack	Recipient	1.00	1.00	CRF
Warfarin sodium, 1 mg/ml	150-ml oral suspension	Recipient	3.00	3.00	CRF
Ward usage					
HDU care	Bed-day	Recipient	14.00	14.00	CRF
ITU care	Bed-day	Recipient	14.00	14.00	CRF
Immunosuppressive medications **(if needed)**					
Azathioprine, 25 mg	28-tablet pack	Recipient	1.00	1.00	CRF
Azathioprine, 50 mg	56-tablet pack	Recipient	3.00	3.00	CRF/Ruth Coxhead, NuTH, March 2015, personal communication
Ciclosporin, 25 mg	30-capsule pack	Recipient	1.00	1.00	CRF
Ciclosporin, 50 mg	30-capsule pack	Recipient	1.00	1.00	CRF
Ciclosporin, 100 mg	30-capsule pack	Recipient	4.00	4.00	CRF/Ruth Coxhead, NuTH, March 2015, personal communication
Mycophenolate mofetil, 500 mg	50-tablet pack	Recipient	3.00	3.00	CRF/Ruth Coxhead, NuTH, March 2015, personal communication
Prednisolone, 1 mg	28-tablet pack	Recipient	1.00	1.00	CRF
Prednisolone, 5 mg	28-tablet pack	Recipient	3.00	3.00	CRF/Ruth Coxhead, NuTH, March 2015, personal communication
Prednisolone, 25 mg	56-tablet pack	Recipient	1.00	1.00	CRF
Prednisolone acetate, 25 mg/ml	1-ml ampoule	Recipient	26.00	26.00	CRF
Sirolimus, 500 µg	30-tablet pack	Recipient	1.00	1.00	CRF

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Sirolimus, 1 mg	30-tablet pack	Recipient	1.00	1.00	CRF
Sirolimus, 2 mg	30-tablet pack	Recipient	2.00	2.00	CRF/Ruth Coxhead, NuTH, March 2015, personal communication
Tacrolimus, 500 µg	50-capsule pack	Recipient	1.00	1.00	CRF
Tacrolimus, 1 mg	50-capsule pack	Recipient	4.00	4.00	CRF/Ruth Coxhead, NuTH, March 2015, personal communication
Tacrolimus, 1 mg	100-capsule pack	Recipient	1.00	1.00	CRF
Tacrolimus, 5 mg	50-capsule pack	Recipient	1.00	1.00	CRF
Other					
Aciclovir, 200 mg	25-tablet pack	Recipient	28.00	28.00	CRF
Amoxicillin (as trihydrate), 500 mg	21-capsule pack	Recipient	1.00	1.00	CRF
Azithromycin (as dihydrate), 250 mg	4-capsule pack	Recipient	1.00	1.00	CRF
Beclomethasone dipropionate, 400 µg/dose	100-dose unit	Recipient	1.00	1.00	CRF
Calcium carbonate (Adcal), 1.5 g	100-tablet pack	Recipient	1.00	1.00	CRF
Cetirizine hydrochloride, 10 mg	30-tablet pack	Recipient	3.00	3.00	CRF
Ciclosporin (NEORAL), 10 mg	60-capsule pack	Recipient	1.00	1.00	CRF
Ciclosporin (NEORAL), 25 mg	30-capsule pack	Recipient	1.00	1.00	CRF
Ciclosporin (NEORAL), 50 mg	50-capsule pack	Recipient	2.00	2.00	CRF
Ciclosporin, 100 mg	30-capsule pack	Recipient	1.00	1.00	CRF
Citalopram (as hydrobromide), 20 mg	28-tablet pack	Recipient	1.00	1.00	CRF
Dapsone, 100 mg	28-tablet pack	Recipient	1.00	1.00	CRF
Dexamethasone, 2 mg	50-tablet pack	Recipient	1.00	1.00	CRF
Doxycycline (as hyclate), 100 mg	8-capsule pack	Recipient	1.00	1.00	CRF
Furosemide, 40 mg	28-tablet pack	Recipient	1.00	1.00	CRF
Hydrocortisone, 10 mg	30-tablet pack	Recipient	5.00	5.00	CRF
Hydrocortisone, 20 mg	30-tablet pack	Recipient	1.00	1.00	CRF
Lisinopril dihydrate, 2.5 mg	28-tablet pack	Recipient	1.00	1.00	CRF
Lisinopril dihydrate, 5 mg	28-tablet pack	Recipient	4.00	4.00	CRF
Methylprednisolone, 2 mg	30-tablet pack	Recipient	1.00	1.00	CRF

continued

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Methylprednisolone (as sodium succinate)	40-mg vial	Recipient	1.00	1.00	CRF
Methylprednisolone (as sodium succinate)	1-g vial	Recipient	1.00	1.00	CRF
Mycophenolic acid (as sodium), 180 mg	120-tablet pack	Recipient	1.00	1.00	CRF
Mycophenolic acid (as sodium), 360 mg	120-tablet pack	Recipient	1.00	1.00	CRF
N-acetylcysteine, 200 mg/ml	10-ml ampoule	Recipient	1.00	1.00	CRF
Perindopril erbumine, 2 mg	30-tablet pack	Recipient	1.00	1.00	CRF
Perindopril erbumine, 4 mg	30-tablet pack	Recipient	1.00	1.00	CRF
Sulfamethoxazole, 400 mg; and trimethoprim, 80 mg (co-trimoxazole)	28-tablet pack	Recipient	1.00	1.00	CRF
Tacrolimus (Prograf), 1 mg	50-capsule pack	Recipient	1.00	1.00	CRF
Tacrolimus (Prograf), 1 mg	100-capsule pack	Recipient	1.00	1.00	CRF
Tinzaparin sodium, 3500 units	0.35-ml pre-filled disposable injection	Recipient	1.00	1.00	CRF
Concomitant medications *Variable costs*					
Treatment					
Aciclovir, 200 mg	25-tablet pack	Recipient	9.00	9.00	CRF p. 111
Adrenaline (base), 100 µg/ml (1 in 10,000)	10-ml pre-filled disposable injection	Recipient	15.00	15.00	CRF p. 111
Alendronic acid (as sodium), 70 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Alfentanil (as hydrochloride), 500 µg/ml	2-ml ampoule	Recipient	2.00	2.00	CRF p. 111
Alfentanil (as hydrochloride), 5 mg/ml	1-ml ampoule	Recipient	9.00	9.00	CRF p. 111
Allopurinol, 300 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Amiloride hydrochloride, 5 mg; and furosemide, 40 mg (co-amilofruse)	56-tablet pack	Recipient	1.00	1.00	CRF p. 111
Amiodarone hydrochloride, 30 mg/ml	10-ml pre-filled disposable syringe	Recipient	60.00	60.00	CRF p. 111
Amiodarone hydrochloride, 100 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Amiodarone hydrochloride, 200 mg	28-tablet pack	Recipient	6.00	6.00	CRF p. 111
Amitriptyline hydrochloride, 10 mg	28-tablet pack	Recipient	2.00	2.00	CRF p. 111
Amlodipine, 5 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Amlodipine, 10 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Amoxicillin (as trihydrate), 500 mg	21-capsule pack	Recipient	1.00	1.00	CRF p. 111
Amoxicillin (as amoxicillin trihydrate), 500 mg; and clavulanic acid (as potassium), 125 mg	21-tablet pack	Recipient	2.00	2.00	CRF p. 111
Amphotericin B, 5 mg/ml	20-lozenge pack	Recipient	2.00	2.00	CRF p. 111
Amphotericin B (as phospholipid complex, 5 mg/ml	20-ml vial	Recipient	2.00	2.00	CRF p. 111
Antiembolism socks	Socks pack	Recipient	1.00	1.00	CRF p. 111
Anti-thymocyte immunoglobulin (rabbit)	25-mg vial	Recipient	20.00	20.00	CRF p. 111
Aspirin, 75 mg	28-tablet pack	Recipient	2.00	2.00	CRF p. 111
Atracurium besilate, 10 mg/ml	5-ml ampoule	Recipient	1.00	1.00	CRF p. 111
Azathioprine, 25 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Azathioprine, 50 mg	56-tablet pack	Recipient	2.00	2.00	CRF p. 111
Azithromycin (as dihydrate), 250 mg	4-tablet pack	Recipient	1.00	1.00	CRF p. 111
Azithromycin (as dihydrate), 250 mg	6-capsule pack	Recipient	9.00	9.00	CRF p. 111
Azithromycin, 500 mg	3-tablet pack	Recipient	1.00	1.00	CRF p. 111
Aztreonam	2-g vial	Recipient	12.00	12.00	CRF p. 111
Bisoprolol fumarate, 1.25 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Bisoprolol fumarate, 2.5 mg	28-tablet pack	Recipient	5.00	5.00	CRF p. 111
Bisoprolol fumarate, 5 mg	28-tablet pack	Recipient	2.00	2.00	CRF p. 111
Bupivacaine hydrochloride, 1 mg/ml	100-ml infusion bag	Recipient	1.00	1.00	CRF p. 111
Calcium carbonate (Adcal), 1.5 g	100-tablet pack	Recipient	1.00	1.00	CRF p. 111
Calcium carbonate, 1.25 g; and colecalciferol, 400 units (Calcichew D3 Forte)	60-tablet pack	Recipient	3.00	3.00	CRF p. 111
Calcium chloride dihydrate, 10%	10-ml pre-filed disposable injection	Recipient	1.00	1.00	CRF p. 111

continued

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Calogen emulsion	500-ml bottle	Recipient	4.00	4.00	CRF p. 111
Carbocisteine, 375 mg	120-capsule pack	Recipient	3.00	3.00	CRF p. 111
Caspofungin (as acetate)	50-mg vial	Recipient	18.00	18.00	CRF p. 111
Ceftazidime (as pentahydrate)	2-g vial	Recipient	11.00	11.00	CRF p. 111
Chlordiazepoxide hydrochloride, 5 mg	100-capsule pack	Recipient	1.00	1.00	CRF p. 111
Chlordiazepoxide hydrochloride (Librium), 10 mg	100-capsule pack	Recipient	1.00	1.00	CRF p. 111
Chlorhexidine gluconate, 4%	500-ml surgical scrub	Recipient	1.00	1.00	CRF p. 111
Chlorhexidine hydrochloride, 500 mg	500-mg pump pack	Recipient	1.00	1.00	CRF p. 111
Chlorhexidine hydrochloride, 1 mg/g; and neomycin sulfate, 5 mg/g (Naseptin)	15-g nasal cream	Recipient	8.00	8.00	CRF p. 111
Chlorhexidine hydrochloride, 10 mg/g; and nystatin, 100,000 units/g (Nystaform)	30-g cream	Recipient	1.00	1.00	CRF p. 111
Chlorphenamine maleate, 10 mg/ml	1-ml ampoule	Recipient	3.00	3.00	CRF p. 111
Chlorpromazine hydrochloride, 25 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Ciclosporin (NEORAL), 25 mg	30-capsule pack	Recipient	1.00	1.00	CRF p. 111
Ciclosporin, 50 mg	30-capsule pack	Recipient	2.00	2.00	CRF p. 111
Ciclosporin, 100 mg	30-capsule pack	Recipient	2.00	2.00	CRF p. 111
Ciprofloxacin (as hydrochloride), 500 mg (Ciproxin)	10-tablet pack	Recipient	3.00	3.00	CRF p. 111
Ciprofloxacin (as hydrochloride), 750 mg	10-tablet pack	Recipient	1.00	1.00	CRF p. 111
Citalopram (as hydrobromide), 20 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Citalopram (as hydrobromide), 40 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Clonidine hydrochloride, 25 µg	112-tablet pack	Recipient	1.00	1.00	CRF p. 111
Codeine phosphate, 8 mg; and paracetamol, 500 mg	30-tablet pack	Recipient	3.00	3.00	CRF p. 111
Codeine phosphate 30 mg and paracetamol, 500 mg	100-tablet pack	Recipient	1.00	1.00	CRF p. 111

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Codeine phosphate, 30 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Codeine phosphate, 60 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Colecalciferol, 500 µg (20,000 units)	15-capsule pack	Recipient	1.00	1.00	CRF p. 111
Colistimethate sodium	1-million-unit vial	Recipient	56.00	56.00	CRF p. 111
Colistimethate sodium	2-million-unit vial	Recipient	28.00	28.00	CRF p. 111
CREON, 25,000 units	100-capsule pack	Recipient	2.00	2.00	CRF p. 111
CREON Micro Pancreatine, 20 g	60.12-mg granules	Recipient	1.00	1.00	CRF p. 111
Cryoprecipitate	8 units	Recipient	1.00	1.00	CRF p. 111
Cyclizine hydrochloride, 50 mg	100-tablet pack	Recipient	3.00	3.00	CRF p. 111
Dapsone, 100 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Diazepam, 2 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Digoxin, 250 µg/ml	2-ml ampoule	Recipient	28.00	28.00	CRF p. 111
Diltiazem hydrochloride, 120 mg	28-capsule pack	Recipient	1.00	1.00	CRF p. 111
Diltiazem hydrochloride, 200 mg	7-capsule pack	Recipient	1.00	1.00	CRF p. 111
Docusate sodium	100-capsule pack	Recipient	1.00	1.00	CRF p. 111
Domperidone (as maleate), 10 mg	100-tablet pack	Recipient	2.00	2.00	CRF p. 111
Dopamine hydrochloride, 40 mg/ml	5-ml ampoule	Recipient	8.00	8.00	CRF p. 111
Dosulepin hydrochloride, 25 mg	28-capsule pack	Recipient	2.00	2.00	CRF p. 111
Doxazosin (as mesilate), 4 mg	28-tablet pack	Recipient	2.00	2.00	CRF p. 111
Doxycycline (as hyclate), 100 mg	8-capsule pack	Recipient	3.00	3.00	CRF p. 111
Enoxaparin sodium, 100 mg/ml	0.4-ml pre-filled disposable injection	Recipient	19.00	19.00	CRF p. 111
Ensure liquid	250 ml	Recipient	1.00	1.00	CRF p. 111
Erythromycin (as lactobionate)	1-g vial	Recipient	18.00	18.00	CRF p. 111
Esomeprazole (as magnesium dihydrate), 40 mg	28-capsule pack	Recipient	2.00	2.00	CRF p. 111
Ethambutol hydrochloride, 400 mg	56-tablet pack	Recipient	2.00	2.00	CRF p. 111
Ezetimibe, 10 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Ethinylestradiol, 30 µg; and gestodene, 75 µg	21-day preparation	Recipient	1.00	1.00	CRF p. 111

continued

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Ferrous sulfate dried, 200 mg	28-tablet pack	Recipient	3.00	3.00	CRF p. 111
Flucloxacillin (as sodium), 500 mg	28-capsule pack	Recipient	8.00	8.00	CRF p. 111
Flucloxacillin (as sodium)	1-g vial	Recipient	5.00	5.00	CRF p. 111
Fluconazole, 50 mg	7-capsule pack	Recipient	7.00	7.00	CRF p. 111
Fluconazole, 200 mg	7-capsule pack	Recipient	11.00	11.00	CRF p. 111
Fluconazole, 2 mg/ml	100-ml solution for infusion bottle	Recipient	12.00	12.00	CRF p. 111
Fluoxetine (as hydrochloride), 20 mg	30-capsule pack	Recipient	1.00	1.00	CRF p. 111
Fluticasone propionate 50 µg	150-unit dose nasal spray	Recipient	1.00	1.00	CRF p. 111
Fluticasone propionate, 250 µg (Flixotide 250 Accuhaler)	60-dose inhaler	Recipient	1.00	1.00	CRF p. 111
Fluticasone propionate, 250 µg; and salmeterol xinafoate, 50 µg (Seretide 250 Accuhaler)	60-dose inhaler	Recipient	1.00	1.00	CRF p. 111
Folic acid, 400 µg	90-tablet pack	Recipient	1.00	1.00	CRF p. 111
Foscarnet sodium, 24 mg/ml	250-ml solution for infusion bottle	Recipient	42.00	42.00	CRF p. 111
Fosfomycin (as sodium)	2-g vial	Recipient	2.00	2.00	CRF p. 111
Fresh-frozen plasma	271-ml bag	Recipient	7.00	7.00	CRF p. 111
Furosemide, 10 mg/ml	2-ml ampoule	Recipient	14.00	14.00	CRF p. 111
Furosemide, 20 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Furosemide, 40 mg	28-tablet pack	Recipient	2.00	2.00	CRF p. 111
Ganciclovir (as sodium)	500-mg vial	Recipient	21.00	21.00	CRF p. 111
Gelatin (Gelofusine)	1-l infusion bag	Recipient	2.00	2.00	CRF p. 111
Gelatin, 140 mg/g; and glycerol, 700 mg/g	4-g supplement pack	Recipient	72.00	72.00	CRF p. 111
Gliclazide (glycoside), 30 mg	56-tablet pack	Recipient	1.00	1.00	CRF p. 111
Gliclazide, 40 mg	28-tablet pack	Recipient	2.00	2.00	CRF p. 111
Glucose anhydrous, 500 mg/ml	50-ml vial	Recipient	168.00	168.00	CRF p. 111
Glyceryl trinitrate, 1 mg/ml	50-ml ampoule	Recipient	10.00	10.00	CRF p. 111
Haloperidol, 5 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Haloperidol, 5 mg/ml	1-ml ampoule	Recipient	248.00	248.00	CRF p. 111
Heparin sodium, 5000 units/ml	1-ml ampoule	Recipient	49.00	49.00	CRF p. 111
Heparin sodium, 5000 units/ml	5-ml ampoule	Recipient	6.00	6.00	CRF p. 111

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Hydroxocobalamin, 1 mg/ml	1-ml ampoule	Recipient	14.00	14.00	CRF p. 111
Hyoscine butylbromide (Buscopan), 10 mg	56-tablet pack	Recipient	3.00	3.00	CRF p. 111
Ibandronic acid (as sodium monohydrate), 50 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Iloprost (as THAM), 10 µg/ml	30 × 1-ml unit-dose vials	Recipient	1.00	1.00	CRF p. 111
Insulin, 3 ml	5 × 3-ml pre-filled disposable injection devices	Recipient	1.00	1.00	CRF p. 111
Insulin aspart, 100 units/ml	5 × 3-ml pre-filled disposable injection devices	Recipient	2.00	2.00	CRF p. 111
Insulin human (as soluble human) (ACTRAPID), 100 units/ml	10-ml vial	Recipient	27.00	27.00	CRF p. 111
Insulin human (as detemir), 100 units/ml (LEMEVIR)	5 × 3-ml pre-filled disposable injection device	Recipient	1.00	1.00	CRF p. 111
Ipratropium bromide, 250 µg/ml	60 × 1 ml unit-dose vial	Recipient	4.00	4.00	CRF p. 111
Ipratropium bromide, 500 µg	500-µg nebuliser solution	Recipient	4.00	4.00	CRF p. 111
Ipratropium bromide, 2.5 mg/2.5 ml	60-unit-dose vial	Recipient	2.00	2.00	CRF p. 111
Ipratropium bromide, 200 µg/ml; and salbutamol (as sulfate), 1 mg/ml (Combivent)	60-unit dose vial	Recipient	9.00	9.00	CRF p. 111
Itraconazole, 100 mg	15-capsule pack	Recipient	10.00	10.00	CRF p. 111
Itraconazole, 10 mg/ml	150-ml oral solution	Recipient	33.00	33.00	CRF p. 111
Labetalol hydrochloride, 100 mg	56-tablet pack	Recipient	1.00	1.00	CRF p. 111
Labetalol hydrochloride, 200 mg	56-tablet pack	Recipient	1.00	1.00	CRF p. 111
Lactulose	300-ml solution	Recipient	1.00	1.00	CRF p. 111
Lansoprazole, 15 mg	28-capsule pack	Recipient	1.00	1.00	CRF p. 111
Lansoprazole, 30 mg	28-tablet pack	Recipient	2.00	2.00	CRF p. 111
Loratadine, 10 mg	30-tablet pack	Recipient	1.00	1.00	CRF p. 111
Levomepromazine maleate, 25 mg	84-tablet pack	Recipient	1.00	1.00	CRF p. 111
Linezolid, 600 mg	10-tablet pack	Recipient	2.00	2.00	CRF p. 111
Loperamide hydrochloride, 2 mg	30-tablet pack	Recipient	2.00	2.00	CRF p. 111

continued

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Lorazepam, 1 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Lymecycline, 408 mg	28-capsule pack	Recipient	1.00	1.00	CRF p. 111
Magnesium oxide, 160 mg	28-capsule pack	Recipient	2.00	2.00	CRF p. 111
Magnesium sulfate heptahydrate, 500 mg/ml	2-ml ampoule	Recipient	98.00	98.00	CRF p. 111
Magnesium sulfate heptahydrate, 500 mg/ml	5-ml ampoule	Recipient	29.00	29.00	CRF p. 111
Magnesium sulfate heptahydrate, 500 mg/ml	4-ml ampoule	Recipient	56.00	56.00	CRF p. 111
Menadiol phosphate (as sodium phosphate), 10 mg	100-tablet pack	Recipient	1.00	1.00	CRF p. 111
Meropenem (as trihydrate)	1-g vial	Recipient	24.50	24.50	CRF p. 111
MEROCAINE	24-lozenge pack	Recipient	1.00	1.00	CRF p. 111
Methylprednisolone (as sodium succinate)	500-mg vial	Recipient	26.00	26.00	CRF p. 111
Methylprednisolone (as sodium succinate)	1-g vial	Recipient	3.00	3.00	CRF p. 111
Metformin hydrochloride, 500 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Metoclopramide hydrochloride, 10 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Metronidazole, 400 mg	21-tablet pack	Recipient	2.00	2.00	CRF p. 111
Midazolam (as hydrochloride), 1 mg/ml	5-ml ampoule	Recipient	2.00	2.00	CRF p. 111
Milrinone (as lactate), 1 mg/ml	10-ml ampoule	Recipient	228.00	228.00	CRF p. 111
Minocycline (as hydrochloride), 100 mg	28-tablet pack	Recipient	2.00	2.00	CRF p. 111
Mirtazapine, 30 mg	28-tablet pack	Recipient	1.00	1.00	BNF 2014[50]
Montelukast (as sodium), 10 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Mometasone furoate, 50 µg	140-unit dose nasal spray	Recipient	1.00	1.00	CRF p. 111
Morphine sulfate, 1 mg/ml	10-mg disposable syringe	Recipient	16.00	16.00	CRF p. 111
Morphine sulfate (Oramorph), 10 mg/5ml	300-ml oral solution	Recipient	1.00	1.00	CRF p. 111
Movicol	30-sachet pack	Recipient	6.00	6.00	CRF p. 111
Moxifloxacin (as hydrochloride), 400 mg	5-tablet pack	Recipient	18.00	18.00	CRF p. 111
Multivitamins	28-capsule pack	Recipient	2.00	2.00	CRF p. 111

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Mupirocin, 20 mg/g	15-g ointment	Recipient	1.00	1.00	CRF p. 111
Micafungin (as sodium)	100-mg vial	Recipient	14.00	14.00	CRF p. 111
N-acetylcysteine, 600 mg	100-tablet pack	Recipient	1.00	1.00	CRF p. 111
Naproxen, 500 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Nebivolol (as hydrochloride), 5 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Nifedipine, 5 mg	84-capsule pack	Recipient	1.00	1.00	CRF p. 111
Nifedipine, 10 mg	84-capsule pack	Recipient	5.00	5.00	CRF p. 111
Noradrenaline base, 1 mg/ml (as noradrenaline acid tartrate, 2 mg/ml)	4-ml ampoule	Recipient	32.00	32.00	CRF p. 111
Nutrison energy multifibre	1000-ml solution	Recipient	28.00	28.00	CRF p. 111
Nystatin, 100,000 units/ml	30-ml oral suspension	Recipient	4.00	4.00	CRF p. 111
Omeprazole (as magnesium), 10 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Omeprazole (as magnesium), 20 mg	28-tablet pack	Recipient	2.00	2.00	CRF p. 111
Omeprazole (as magnesium), 40 mg	28-capsule pack	Recipient	3.00	3.00	CRF p. 111
Omeprazole (as sodium)	40-mg vial	Recipient	24.00	24.00	CRF p. 111
Ondansetrol (as hydrochloride), 2 mg/ml	1-ml ampoule	Recipient	1.00	1.00	CRF p. 111
Ondansetron (as hydrochloride), 4 mg	30-tablet pack	Recipient	3.00	3.00	CRF p. 111
Oxycodone hydrochloride, 5 mg	56-tablet pack	Recipient	2.00	2.00	CRF p. 111
Oxycodone hydrochloride, 10 mg	56-capsule pack	Recipient	1.00	1.00	CRF p. 111
Pabrinex vitamin B substances with ascorbic acid, 250 mg/10 ml	2 × 5-ml ampoule	Recipient	2.00	2.00	CRF p. 111
Packed red blood cells	274-ml bag	Recipient	61.00	61.00	CRF p. 111
Paracetamol, 500 mg	32-tablet pack	Recipient	2.00	2.00	CRF p. 111
Paracetamol, 1 g	10 mg/ml 100-ml vial	Recipient	28.00	28.00	CRF p. 111
Peppermint water	100-ml solution	Recipient	1.00	1.00	CRF p. 111
Perindopril erbumine, 4 mg	30-tablet pack	Recipient	1.00	1.00	CRF p. 111
Phenoxymethylpenicillin (as potassium), 250 mg	28-tablet pack	Recipient	2.00	2.00	CRF p. 111
Phosphate	500-ml bottle	Recipient	1.00	1.00	CRF p. 111

continued

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Piperacillin (as sodium), 4 g; and tazobactam (as sodium), 500 mg (Tazocin)	4.5-g vial	Recipient	59.00	59.00	CRF p. 111
Platelets	250-ml bag	Recipient	134.00	134.00	CRF p. 111
Posaconazole, 100 mg	96-tablet pack	Recipient	2.00	2.00	CRF p. 111
Potassium bicarbonate, 400 mg; and potassium chloride, 600 mg (Sando-K)	20 tablets	Recipient	2.00	2.00	CRF p. 111
Potassium chloride, 150 mg/ml	10-ml ampoule	Recipient	14.00	14.00	CRF p. 111
Pravastatin sodium, 10 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Pravastatin sodium, 20 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Pravastatin sodium, 40 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Prednisolone, 5 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Pregabalin, 25 mg	56-capsule pack	Recipient	1.00	1.00	CRF p. 111
Pregabalin, 50 mg	84-capsule pack	Recipient	2.00	2.00	CRF p. 111
Pregabalin, 75 g	56-capsule pack	Recipient	2.00	2.00	CRF p. 111
Pregabalin, 100 mg	84-capsule pack	Recipient	1.00	1.00	CRF p. 111
Prochlorperazine maleate, 3 mg	5 × 10-tablet pack	Recipient	1.00	1.00	CRF p. 111
Propofol, 5 mg/ml	20-ml ampoule	Recipient	2.00	2.00	CRF p. 111
Propofol, 10 mg/ml	20-ml ampoule	Recipient	6.00	6.00	CRF p. 111
Propofol, 10 mg/ml	50-ml pre-filled disposable injection	Recipient	3.00	3.00	CRF p. 111
Ramipril, 2.5 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Ramipril, 5 mg	28-capsule pack	Recipient	1.00	1.00	CRF p. 111
Ranitidine (as hydrochloride), 25 mg/ml	2-ml ampoule	Recipient	6.00	6.00	CRF p. 111
Ranitidine (as hydrochloride), 150 mg	60-tablet pack	Recipient	2.00	2.00	CRF p. 111
Ranitidine (as hydrochloride), 300 mg	30-tablet pack	Recipient	1.00	1.00	CRF p. 111
Remifentanil (as hydrochloride)	5-mg vial	Recipient	3.00	3.00	CRF p. 111
Risperidone, 500 µg	20-tablet pack	Recipient	2.00	2.00	CRF p. 111
Risperidone, 2 mg	60-tablet pack	Recipient	1.00	1.00	CRF p. 111
Salbutamol (as sulfate), 2.5 mg/2.5 ml	20-unit dose nebuliser	Recipient	6.00	6.00	CRF p. 111

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Salbutamol (as sulfate), 200 µg	100-dose unit inhaler	Recipient	1.00	1.00	CRF p. 111
Sennoside B (as sennosides), 7.5 mg	60-tablet pack	Recipient	1.00	1.00	CRF p. 111
Sildenafil (as citrate), 25 mg	4-tablet pack	Recipient	7.00	7.00	CRF p. 111
Sodium chloride, 0.9%	20 × 2.5-ml spray	Recipient	9.00	9.00	CRF p. 111
Sodium chloride, 600 mg	100-tablet pack	Recipient	1.00	1.00	CRF p. 111
Sodium cromoglycate, 5 mg/dose	112-unit dose inhaler	Recipient	1.00	1.00	CRF p. 111
Sodium dihydrogen phosphate anhydrous, 1.936 g	100-tablet pack	Recipient	2.00	2.00	CRF p. 111
Sodium valproate, 200 mg	100-tablet pack	Recipient	13.00	13.00	CRF p. 111
Strepsils	24-lozenge pack	Recipient	1.00	1.00	CRF p. 111
Sulfamethoxazole, 400 mg; and trimethoprim, 80 mg (co-trimoxazole)	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Tadalafil, 20 mg	8-tablet pack	Recipient	4.00	4.00	CRF p. 111
Tamsulosin hydrochloride, 400 µg	30-capsule pack	Recipient	2.00	2.00	CRF p. 111
T.E.D. compression socks/hose (knee length)	Stocking	Recipient	1.00	1.00	CRF p. 111
Teicoplanin	400-mg vial	Recipient	21.00	21.00	CRF p. 111
Theophylline (Uniphyllin), 200 mg	56-tablet pack	Recipient	1.00	1.00	CRF p. 111
Thiamine hydrochloride, 100 mg	100-tablet pack	Recipient	1.00	1.00	CRF p. 111
Tiotropium (as bromide), 18 µg	30-capsule pack	Recipient	1.00	1.00	CRF p. 111
Tobramycin, 60 mg/ml	56 × 5 ml–300 mg unit	Recipient	11.00	11.00	CRF p. 111
Tobramycin, 75 mg/ml	56 × 4-ml nebuliser	Recipient	1.00	1.00	CRF p. 111
Tramadol hydrochloride, 50 mg	30-capsule pack	Recipient	1.00	1.00	CRF p. 111
Tramadol hydrochloride, 50 mg	60-capsule pack	Recipient	3.00	3.00	CRF p. 111
Tramadol hydrochloride, 100 mg	60-capsule pack	Recipient	2.00	2.00	CRF p. 111
Ursodeoxycholic acid, 150 mg	60-tablet pack	Recipient	1.00	1.00	CRF p. 111
Ursodeoxycholic acid, 300 mg	60-tablet pack	Recipient	2.00	2.00	CRF p. 111

continued

TABLE 51 NHS resource use: detailed table (*continued*)

Resource or intervention	Unit	Patient details	Mean usage in standard donor lung transplantation	Mean usage in EVLP transplantation	Resource source
Valaciclovir (as hydrochloride), 500 mg	42-tablet pack	Recipient	2.00	2.00	CRF p. 111
Valganciclovir (as hydrochloride), 450 mg	60-tablet pack	Recipient	2.00	2.00	CRF p. 111
Vancomycin (as hydrochloride)	1-g vial	Recipient	2.00	2.00	CRF p. 111
Vitamin B compound strong	28-tablet pack	Recipient	2.00	2.00	CRF p. 111
Vitamins A, D and E	30-capsule pack	Recipient	1.00	1.00	CRF p. 111
Multivitamins	100-tablet pack	Recipient	1.00	1.00	CRF p. 111
Voriconazole, 200 mg	28-tablet pack	Recipient	3.00	3.00	CRF p. 111
Warfarin sodium, 3 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111
Water for injections	5-ml ampoule	Recipient	1.00	1.00	CRF p. 111
Zopiclone, 3.75 mg	28-tablet pack	Recipient	1.00	1.00	CRF p. 111

CO_2, carbon dioxide; N_2, nitrogen; ODA, operating department assistant.

Appendix 8 Trial documentation

Participant Information Sheet Main Study v 5.0, 24 May 2013

To be printed on the local trust headed paper

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

Participant Information Sheet Version 5.0

You are being invited to take part in our research study as you have a severe lung disease that makes you a candidate for a lung transplant. Before you decide if you want to take part, it is important for you to understand why the research is being done and what is involved in taking part.

One of our research team will go through this information sheet with you and answer any questions you have about what the study involves, how your information will be used and what the possible benefits and risks of taking part are. Please take time to read the following information carefully. Talk to others about the study if you wish. Please ask if there is anything that is not clear or if there is anything you would like more information about. Take time to decide if you wish to take part.

Part 1 tells you about the purpose of this study and what will happen if you take part.

Part 2 gives you general information about how the study will be conducted.

PART 1
Study Summary
Each year a number of patients on the transplant waiting list do not survive long enough for suitable matching donor lung(s) to become available.

The shortage of organ donors in the United Kingdom has made it even more difficult for those waiting for lung transplant, as donor lungs are very delicate and often deteriorate due to events that happen before the lungs are removed from the donor. The effect of this is that currently only 1 in 5 or 20% of the potential donor lungs available in the UK are currently acceptable for use in lung transplant surgery. Despite a lot of effort to promote organ donation recently, there remains a major shortage of usable donor lungs for UK patients waiting for lung transplantation.

In this study, a new technique called **Ex-Vivo Lung Perfusion** or **EVLP** will be tested to find out how effective it is at increasing numbers of lung transplants performed, by turning previously unusable donor lungs into lungs which can be safely used for transplant. EVLP involves attaching the donor lungs, after they are removed from the donor, to a modified heart-lung bypass machine for several hours. The modified bypass machine pumps a specialised nutrient liquid through them, while at the same time provides the lungs with oxygen via a breathing machine. The EVLP technique has been used successfully in an increasing number of lung transplant centres around the world to improve the condition of

otherwise unusable donor lungs so that they can be given successfully to patients awaiting lung transplant.

Although, there are promising early results, the EVLP technique has not been tested in a controlled clinical trial that assesses whether EVLP is an effective way to increase the number of donor lungs available for lung transplantation. The **DEVELOP-UK** study will aim to answer this question.

The UK is in a very good position to conduct this study as most of the UK lung transplant centres have already developed some experience with the EVLP technique with 17 patients on UK lung transplant waiting lists receiving EVLP assessed and improved donor lungs. By August 2011, this meant 25% of lung transplants performed worldwide using EVLP have been done in the UK. Our experience to date suggests that approximately half of the donor lungs treated with EVLP can be improved successfully for transplant. This means many of the 80% of donor lungs currently found to be unusable may have the potential to be improved sufficiently to be used for lung transplantation.

What is the purpose of the study?
It has been shown that the current method used to assess whether potential donor lungs are usable for lung transplantation is not optimal. This suggests that many donor lungs deemed unusable could in fact be suitable for lung transplantation. EVLP may therefore allow many previously unusable donor lungs to be carefully assessed and improved for safe use in lung transplantation. This would help to significantly increase the chances of a suitable donor organ being found for patients on the lung transplant waiting list.

The **DEVELOP-UK** study has been designed to carefully assess the results of lung transplants performed with donor lungs which have been assessed and improved with EVLP compared to those done with standard donor lungs.

Donor lungs offered but considered not suitable for standard transplant, will be transferred to the transplant centre where they will be placed on the EVLP system. The donor lungs will then be monitored for up to 4 hours to measure how well their function improves and to make sure there is no irreversible damage present. If their function improves to a level where they can pass a rigorous assessment, the donor lungs are then offered to a patient on the lung transplant waiting list who has given their prior agreement to take part in the study.
The study will be deemed a success if it shows that survival in the first 12 months after lung transplant is as good in patients who have received EVLP improved donor lungs as in patients who received standard donor lungs.

The DEVELOP-UK research team will also look to see if there are any more early complications, such as a longer stay on intensive care, more frequent infections or more episodes of transplant rejection, in patients who have received EVLP improved donor lungs compared to standard donor lungs.

A Quality of Life Questionnaire will be used to assess whether changes in quality of life in the first post-transplant year in patients who received EVLP assessed and improved donor lungs are similar to those in patients who received standard donor lungs.

Finally, the cost to the NHS of using the EVLP technology will be calculated. All the information generated in the study will be used by the NHS commissioners, who pay for UK

transplant services, to decide if this technique can be adopted as part of normal practice in the future.
In addition, by carrying out **detailed interviews** with some of the patients agreeing to take part in the DEVELOP-UK study, the research team will try to understand the experiences and any concerns expressed by patients about undergoing transplantation with EVLP donor lungs. This will enable clinicians to address effectively any patient concerns in the future.

Why have I been invited?
You have been invited to participate in this study because you are 18 years old or over and you have either already been accepted onto an active lung transplant waiting list in the UK or are under serious consideration for potential lung transplantation in one of the adult lung transplant centers.

Do I have to take part?
It is up to you to decide whether to take part in the study. You do not have to participate if you do not wish to. However, if you do decide to participate, the research team will describe carefully to you what the study involves and give you this information sheet to keep. The team will explain how decisions are made about donor lungs' usability for lung transplantation and why the majority are felt unusable for standard lung transplantation.

They will also explain which unusable donor lungs are suitable for EVLP and how their function after EVLP is assessed to decide if they have become usable for lung transplant. The donor lungs assessed and improved by EVLP have to reach the same level of function as standard lungs before they will be considered usable for lung transplantation. The research team will provide firm reassurance that if donor lungs do not improve sufficiently after EVLP they will not be used for transplantation.

All the questions you have about the study will be answered by the team. You will be given time to think this over and talk to your family and friends about it. If you agree to take part, you will be asked to sign either an expression of interest form and then a consent form or the consent form itself depending on whether the discussion with you has happened in person or over the telephone.

As the time between going on the waiting list and getting a lung transplantation varies widely and can in some cases exceed 12 months, you will be asked to reconfirm your consent when you are called in and offered transplantation with an EVLP assessed and improved donor lung(s). However, if you sign the consent form on the day of transplant you do not need to reconfirm your consent. The clinical transplant team will inform you whether you are to receive an EVLP assessed and improved donor lung or a standard donor lung. You will not be asked to reconfirm your consent if you have signed the consent form prior to being called in for transplantation and are offered transplantation with standard donor lung(s).

If you decide to take part you are still free to withdraw from the study at any time and you do not have to give a reason. This will not affect the standard of care you receive either now or in the future. If you decide not to participate, you will have equal access to donor lungs for standard transplant but would not be considered for donor lungs that have undergone EVLP assessment and improvement.

What will happen to me if I take part?

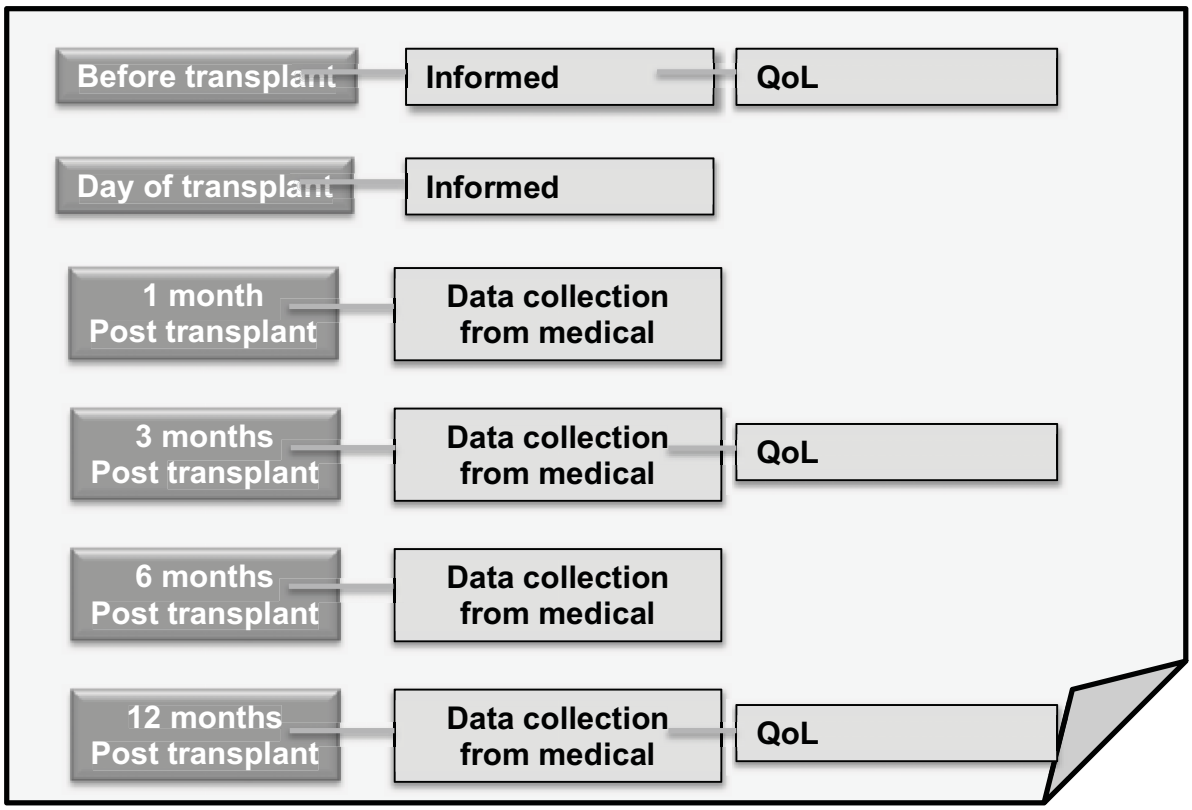
This is an observational study. It means that no extra tests or procedures will need to be done on you. The EVLP process to assess whether the donor lungs have improved enough for use in a lung transplant is performed before any transplant surgery is started.

You will not need any extra clinical visits to hospital or your GP as a result of being in the study. All your hospital visits will be arranged by the transplant team as a part of routine care after lung transplant. Collection of your information for the purposes of the study will be coordinated with your routine post-lung transplantation clinic visits.

The research team will ask if you are willing for them to collect data that can be extracted from your medical records. If you were to *lose capacity* (become unable to decide whether to carry on with the study) over the follow-up period, the research team will aim to continue data collection from your medical notes. This will not impact on the standard of medical care you receive. Once you have signed an expression of interest form or informed consent form for the DEVELOP-UK we will ask you to complete a Quality of Life Questionnaire. It will take you approximately 15 to 20 minutes.

When you are called in for possible transplantation, the transplant team will explain to you whether you are to receive EVLP-assessed and improved donor lung(s) or standard donor lung(s). If you have signed consent form before the day of transplant you will be asked whether you wish to reconfirm your consent and continue to participate in the study if you are offered EVLP assessed and improved donor lung(s) but not for standard donor lung(s). If you sign consent form on the day of transplant you do not need to reconfirm your consent. If you decide not to continue in the study then any possible transplant with EVLP assessed and improved lungs will not go ahead.

Following lung transplantation you will be asked to complete the same Quality of Life Questionnaire 3 months and 12 months after your lung transplant (see the diagram below).



Expenses and payments

This is an observational study. As all the information needed for the study will be collected when you are already attending the transplant centre for routine clinic visits, there are no payments made to you to participate in the DEVELOP-UK study.

What will I have to do?

Please consider carefully the clinical and research aspects of the study.

The study visits will be coordinated to coincide with your routine clinic visits at 1 month, 3 months, 6 months and 12 months after your lung transplantation. The data we collect for this study will be part of your routine follow up care and recorded from your medical notes and from computerised results in the hospital.

If you decide to participate in the DEVELOP-UK you will need to complete a Quality of Life Questionnaire before lung transplantation, and then at 3 and 12 months after receiving your lung transplant.

If you have been taking part in another clinical or drug study in the past 12 months please discuss this with the study doctors. It may not prevent you from participating in the DEVELOP-UK study. After undergoing lung transplantation you should not participate in any clinical study that might affect your standard post-transplant care for 12 months. After this 12 months post-transplant period you can participate in any clinical or drug studies as you wish. Please contact the study doctor if you have any questions. If you wish to participate in any observational studies before or after lung transplant please discuss it with the study doctor.

What are the alternatives for diagnosis or treatment?

For selected patients suffering from long lasting severe lung disease, lung transplantation is the only realistic therapeutic option.

What are the possible disadvantages and risks of taking part?
The main risk of taking part in the study is that you might receive an EVLP assessed and improved donor lung that does not function well after transplant. This could mean requiring a longer stay in the intensive care unit to give artificial support to the transplanted lung or even death. However, similar risks also exist for standard donor lungs as a significant proportion of standard donor lungs do not function well after lung transplant. The DEVELOP-UK study is designed to address the question as to how effective the EVLP technique is at safely increasing availability of donor lungs. By May 2013, worldwide experience in more than 150 patients suggests that transplanted EVLP assessed and improved lungs are likely to work as effectively as standard donor lungs. Any possible risks of taking part in the study should be balanced against the risk of not receiving a lung transplant at all because a standard donor lung has not been available in adequate time.

Transplanted lungs, whether standard or EVLP assessed and improved, always remain vulnerable to the possibility of rejection and one of the main risk factors is low immunosuppression levels. Therefore prior to being accepted onto the transplant list you were counselled about the absolute necessity to comply with your treatment and to attend all arranged post-transplant follow-up appointments.

Topics in the Quality of Life Questionnaire that you will be asked to complete will include your views about how much your condition affects your health, your regular daily activities and your emotional state. It is possible that you may find some of these questions upsetting due to their nature. It also includes such topics as bodily pain, depression and your social life. Please be assured that all of your responses are entirely confidential.

What are the possible benefits of taking part?
By agreeing to take part in the DEVELOP-UK study you may have access to a larger number of potential matching donor lungs for your transplant. This is because EVLP allows otherwise unusable donor lungs to be meticulously assessed and potentially improved for successful lung transplantation. This technology therefore may have the capacity to reduce the time an individual spends on the waiting list for lung transplant.

What happens when the research study stops?
This is an observational study. Therefore there will be no change to your standard medical care throughout and after the study.

What if there is a problem?
Any complaint about the way you are dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

Will my taking part in the study be kept confidential?
Yes. The research team will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

PART 2
General information

What if relevant new information becomes available?
If new information about the EVLP technique, that might affect the way the study is conducted, becomes available, your study doctor will tell you and discuss whether you should continue in the study. If you decide not to carry on, your standard medical care will not be affected and you will have equal access to standard donor lungs for transplant.

What will happen if I don't want to carry on with the study?
You can withdraw from the study at any time, and without giving a reason. However, we might ask you if you are happy for us to record why you have decided to withdraw.

If you initially agreed to participate in DEVELOP-UK but then decided to withdraw on the day of transplantation, then any possible transplant with EVLP assessed and improved lungs will not go ahead. If you are to receive standard donor lungs but decided to withdraw from the study then no follow up data will be collected from your medical notes. If you have signed initial consent, then (if necessary) reconfirmed your consent on the day of transplant to receive EVLP assessed and improved donor lung(s) and then received the transplant but decided to withdraw later, data collected up to the point of withdrawal will be retained.

What if there is a problem?
If you have a concern about any aspect of this study, you should speak to the study doctor who will do their best to answer your questions (add local contact details). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details of how to complain can be obtained by contacting (add local contact details (Trust PALS))

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for legal action for compensation; however you may need to meet your own legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate). NHS Indemnity does not offer no-fault compensation (i.e. for harm that is not anyone's fault). Neither the sponsor (The Newcastle upon Tyne Hospitals NHS Foundation Trust) who has undertaken to manage the study, nor the management of the hospital/research centre you are attending for your routine treatment, is able to agree in advance to pay compensation for non-negligent harm.

Will my taking part in this study be kept confidential?
All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be identified.

The data that is collected from your clinical notes will be entered onto a secure computer database. Access to this database will be password protected and available to your doctors and the research staff for the purpose of the study. All data stored on the computer will be coded and your name will not appear. You will be given a unique study number under which all data and test results will be entered. These data will be analysed to find out how well

EVLP assessed and improved donor lungs function in comparison with standard donor lungs after transplantation. The analysis of the data we obtain from Quality of Life Questionnaire will be used to measure the health related costs of the EVLP technique.

If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorised persons from the sponsor of this study (The Newcastle upon Tyne NHS Foundation Trust) or their representatives. They may also be looked at by authorised people from regulatory authorities and the Newcastle Clinical Trials Unit to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and will do their best to meet this duty. All the information about your participation in this study will be kept confidential. All data will be stored for at least 15 years and then disposed of securely. Your data will not leave the UK nor will it be passed onto anyone outside of this study.

Involvement of the General Practitioner/Family doctor (GP)
We will ask you specifically if you want your GP to be informed about your participation in DEVELOP-UK. You can refuse for your GP to be informed without giving any reasons.

What will happen to any samples I give?
No samples will be collected from you that are not part of your standard medical care. However at the start and at the end of the EVLP process the research team will take a small sample of lung tissue from the donor lung. These samples will be studied by the research team themselves to help understand how EVLP is working. Some of this work might be done in partnership with other academic organisations or companies both inside and outside the UK. No identifiable personal information will accompany any samples.

What will happen to the results of the research study?
The results from this study will be published in widely read medical journals which review the quality of the results and will be presented at national and international medical meetings. The results will also be reported to the Sponsor (The Newcastle upon Tyne NHS Foundation Trust) and Funders (National Institute for Health Research Health Technology Assessment Programme in the Department of Health and Cystic Fibrosis Trust), and will be available on the study website www.develop-uk.net. As a participant in the trial you will not be identified from any publication, study report or presentation. You will be informed about your contribution to the study at the end of the study, including a summary of the results.

Who is organising and funding the research?
The research is being organised and delivered by a team of researchers from across the UK including representatives from all 5 adult lung transplant centres. Professor Andrew Fisher from The Institute of Transplantation at Freeman Hospital, Newcastle and Newcastle University is the Chief Investigator and the Newcastle University Clinical Trials Unit is managing the study. The work is supported by a Project Grant awarded from the Department of Health via the National Institute for Health Research Health Technology Assessment Programme and by funding from The Cystic Fibrosis Trust UK.

Who has reviewed the study?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favorable opinion by NRES Committee North East - Sunderland. The Chief Executive of the Newcastle upon Tyne Hospitals NHS Foundation Trust has agreed to provide indemnity for

the study in terms of its management. The conduct of the study at [please add Trust/centre name], for your treatment has indemnity cover through the normal NHS schemes.

The NHS is trying to improve the quality of clinical and research standards. This is being achieved through 'clinical governance'. As part of this process, this study may be reviewed by a clinical governance team. Such a team would need to look at any information that you provide us with, to make sure that the research was carried out in accordance with proper procedures.

Further information and contact details
For further information about the study you can speak to one of the Study Team:

Dr: PI's name + contact details
Research Nurse: Name + contact details

Alternatively you can speak to the Independent contact: please add local independent contact.

Emergency out of hours contact details: Name and contact details

Thank you for taking the time to read this information sheet

Participant Information Sheet Interview Study v 1.0, 1 November 2011

To be printed on the local trust headed paper

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

Interview Study

Participant Information Sheet Version 1.0

You are being contacted because you expressed an interest in receiving more information about the interview component of the DEVELOP-UK study. We are sending you this participant information sheet to help you to decide whether you would be willing to take part in an interview about your views and experiences. This is entirely **optional** and you are under no obligation to take part. If you decide you do not want to be interviewed this will have no effect on your involvement in the rest of the DEVELOP-UK study. **If you do not want to take part, you do not need to do anything further.** We will not contact you again about this matter. However, if you are still willing to take part in an interview we would like to give you more information to help you to decide.

To help you to decide if you want to take part in the interview study, it is important that you understand why the research is being carried out and what it will involve for you. Please take time to read the following information carefully, and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. If, having read this information, you are interested in taking part in the interview study please either call the research team directly on 0191 222 3805 or return the form (attached at the end of the information sheet) in the enclosed Stamped Addressed Envelope and they will call you to arrange the interview.

Part 1 tells you the purpose of this interview study and what will happen to you if you take part.
Part 2 gives you general information about the conduct of the study.
Please ask us if there is anything that is not clear.

PART 1
Study Summary

Ex-vivo lung perfusion or EVLP is a new technique that allows assessment and improvement of poorly functioning donor lungs so that they can be safely used in lung transplantation. To date research related to people's experiences of receiving a donor organ is very limited. We know that waiting for a transplantation impacts on patients and their families and we would like to speak with patients about their experiences. We also do not know what patients think about EVLP. Therefore we would like to conduct interviews with patients either before or after lung transplantation, and with some patients both before and after. The interviews will help the research team to understand your experiences of waiting for lung transplantation, your hopes and expectations of EVLP and, if you receive EVLP assessed and improved lung, your views of living with an EVLP transplant.

What is the purpose of the study?
The aim of this interview is to understand more about your views of EVLP before and after lung transplantation.
Why have I been invited?
You have been invited to participate in this sub-study because you have expressed an interest in taking part in the DEVELOP-UK Study.

Do I have to take part?
It is up to you to decide whether to join this interview sub-study. If you do decide to participate, we will describe carefully what is involved with the study and give this information sheet to keep. You will be given time to think this over and talk to your family and friends about it.

This interview study is purely optional – you do not have to take part. It would not affect your participation in the DEVELOP-UK study. If you agree to take part, you can withdraw at any time without giving a reason and you will not be asked to participate in this interview study again.

What will happen to me if I take part?
Once you have indicated that you are willing to be interviewed then one of the DEVELOP-UK research team from the Institute of Health and Society, Newcastle University will contact you by telephone and discuss the interview study with you and will answer any questions you have.

We will ask you whether you prefer to be interviewed face to face either at your home or in a suitable hospital room, or you may choose to be interviewed by telephone. If you choose to be interviewed in the hospital we will arrange for the interviews to take place during your usual appointments at the transplant centre.
We will ask you to sign a consent form which shows that you agree to take part. If you decide to be interviewed face to face, the consent form will be signed before the interview occurs. You can invite your relative or another person who cares for you to participate in an interview with you. A separate consent form will be provided for her/him. If you decide to have the interview by telephone we will go through the consent form with you and record you verbal consent.

We are approaching you as we would like to speak to people at different times; we would like to speak to people who are waiting for a transplant or who have already had a lung transplantation operation. Interviews will last approximately 45-60 minutes although may be slightly longer or shorter.

If you are waiting for a lung transplant we would like to talk about the following topics during the interview:

- Your view of your health and experience of living with your condition
- Your experience of waiting for lung transplantation
- Your understandings of EVLP and its acceptability in comparison with other donor lungs
- Your hopes and expectations for EVLP

If you have already had a lung transplant we would like to talk about the following topics during the interview:

- Recollection of your health and experiences before the operation
- Your accounts of waiting for a transplant
- Your views and experiences of receiving and living with an EVLP transplant (if you received EVLP assessed and improved donor lung)

All interviews will be recorded. This is to help the researcher listen to the discussion and accurately record what is being said. These tapes will be transcribed and the study team will securely store both the tape and transcription. All data will be confidential and all data will be anonymised.

Expenses and payments

The interviews performed in this study will be conducted either during a routine visit to the transplant clinic, in your own home or over the telephone. We will therefore not be able to pay for you to participate in the Interview study for DEVELOP-UK. If a telephone interview is chosen then the researcher will telephone you at our expense.

What will I have to do?

Please consider carefully all aspects of the Interview Study. This study is purely optional and will not affect your participation in DEVELOP-UK. You can withdraw at any time without giving any reason.

If you like, a relative or another person who cares for you can also be interviewed with you. If you decide to take part you and your relative or person who cares for you will also need to sign a consent form. Once we receive your signed form indicating you are interested in taking part in the Interview Study, one of our research team members will contact you to arrange the time of the interview either at a place of your choice or over the telephone. Each interview will last approximately 45-60 minutes.

What are the possible disadvantages and risks of taking part?

You may find some of the topics and issues discussed during interviews upsetting. We would like to know how much your health, regular daily activities and personal relationships were affected before and after lung transplantation, and we will discuss specifically your views and experiences of EVLP.

Please be reassured that all of your responses are entirely confidential. If you do become upset at any time you can choose to stop the interview immediately. We will only continue with the interview if you are happy for us to do so.

What are the possible benefits of taking part?

There are no direct benefits from taking part in this interview study but it will help us to understand what you think and expect from EVLP. Understanding what patients think plays a very important part in the possible successful introduction of this new EVLP technique to lung transplantation in the UK.

What if there is a problem?

Any complaint about the way you have been dealt with during the Interview study will be addressed. Detailed information on this is given in Part 2.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

PART 2
General information

What will happen if I don't want to carry on with the Interview Study?
You can choose to stop the interview at any time for any reason, and without giving a reason. If you do so you can choose whether to have the earlier part of the interview destroyed, or whether you are willing for the research team to use the data they have collected.

If you are approached whilst you are waiting for transplantation, there is a chance we will contact you again after your transplant operation to find out more about your experience.

You can withdraw from the Interview study at any time for any reason, and without giving a reason. If you decided to withdraw, data collected up to the point of withdrawal will be retained.

What if there is a problem?
If you have a concern about any aspect of this study, you should speak to the study researcher who will do their best to answer your questions (Dr Catherine Exley, Institute of Health and Society, Newcastle University [redacted]).

If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details of how to complain can be obtained by contacting (Dr Catherine Exley, Institute of Health and Society, Newcastle University [redacted]).

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for legal action for compensation; however, you may need to meet your own legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate). NHS Indemnity does not offer no-fault compensation (ie. for harm that is not anyone's fault). Neither the sponsor (The Newcastle upon Tyne Hospitals NHS Foundation Trust) who has undertaken to manage the study, nor the management of the hospital/research centre you are attending for your routine treatment, is able to agree in advance to pay compensation for non-negligent harm.

Will my taking part in this study be kept confidential?
All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised.
The data we collect from your interviews will be entered onto a secure database. Access to this database will be password protected. All data stored on the computer will be coded and your name will not appear. The analysis of your interviews will help us to improve future practice development.

If you join the interview study, some parts of your interviews may be looked at by authorised persons from the sponsor of this study (Newcastle upon Tyne NHS Foundation Trust) or their representatives. However, none of your personal information will be linked with extracts of your interview. They may also be looked at by authorised people from regulatory authorities and the Newcastle Clinical Trials Unit to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and will do their best to meet this duty. All the information about your participation in this study will be

kept confidential. All data will be stored for at least 15 years and then disposed of securely. All the information collected will be managed by the study team only and will be destroyed after a period of fifteen years.

What will happen to the results of the research study?
The results from this interview study will be published in professional journals where the quality of the results will be assessed. In addition results will be presented at national and international meetings. The results will also be reported to the Sponsor (the Newcastle upon Tyne NHS Foundation Trust) and Funder (National Institute for Health Research Technology Assessment Programme in the Department of Health and the Cystic Fibrosis Trust), and will be available on the study website www.develop-uk.net. As a participant in interview study you will not be identified from any publication, study report or presentation.

A summary of the findings of the interview study will be made available to you at the end of the whole study.

Who is organising and funding the research?
The Interview study is being led by Dr Catherine Exley who is based at Newcastle University's Institute of Health & Society. The people who are doing the interviews either work directly with Dr Exley at the University or are nurses at one of the transplant centres. The work is supported by a Project Grant awarded from the National Institute for Health Research Health Technology Assessment Programme and the Cystic Fibrosis Trust.

Who has reviewed the study?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by NRES Committee North East - Sunderland. The Chief Executive of the Newcastle upon Tyne Hospitals NHS Foundation Trust has agreed to provide indemnity for the study in terms of its management. The conduct of the study at (please add Trust/centre name), for your treatment has indemnity cover through the normal NHS schemes.

The NHS is trying to improve the quality of clinical and research standards. This is being achieved through 'clinical governance'. As part of this process, this study may be reviewed by a clinical governance team. Such a team would need to look at any information that you provide us with to make sure that the research was carried out in accordance with proper procedures.

Further information and contact details
For further information about the study you can speak to one of the Study Team:
Dr Catherine Exley
Institute of Health and Society
Newcastle University
[redacted]
Research Nurse: Name + contact details.
Alternatively you can speak to the Independent contact: please add local independent contact.
Emergency out of hours contact details: Name and contact details

Thank you for taking the time to read this information sheet.

Please return this page to us in the enclosed stamped addressed envelope if you are willing to be interviewed

I am interested in taking part in the Interview study.

I am happy for a member of the research team at the Institute of Health and Society, Newcastle University to contact me to arrange a convenient time for me to take part.

Please contact me:

Name: ----------

Address: ----------

Telephone: ----------

Appendix 9 Trial letters

Letter to GP v 1.0, 1 November 2011

To be printed on the local trust headed paper

Date:

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

Dear Dr

Patient's Name: _____

Address: _____

_____

DOB: _____

Your patient has agreed to participate in the DEVELOP-UK study.

This observational study aims to examine survival during the first 12 months after lung transplantation in recipients of ex-vivo lung perfusion (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.

DEVELOP-UK will also evaluate early clinical outcomes and changes in Quality of Life in the treatment and control group in their first post-transplant year; assess (by statistical modeling) the survival benefit for waiting list patients and determine if EVLP is a cost-effective intervention for the NHS to support as standard care within UK lung transplant centers in the future.

An optional qualitative sub-study will be based on interviews with patients awaiting lung transplantation (and their carers) and with patients receiving EVLP reconditioned lungs to explore their attitudes towards and experiences of EVLP.

Please find enclosed a copy of the information sheet given to your patient.
Please do not hesitate to contact me for any queries relating to the study, or to report any untoward symptoms experienced by patient. I can be contacted on the following telephone number:

(Name of local PI and contact phone number)

Yours sincerely

Update on DEVELOP-UK Letter to Participants v 1.0, 24 May 2013

To be printed on Trust Headed paper

Update on DEVELOP-UK Study
Donor Ex-vivo Lung Perfusion in United Kingdom Lung Transplantation

Date
Dear XXXX
I am writing to update you with some new information about the **DEVELOP-UK** study.
You will recall that this study is running in all the United Kingdom lung transplant centres and is designed to investigate a technique called ex-vivo lung perfusion (or EVLP). The study is assessing how effective EVLP is at improving donor lungs that are currently not suitable for transplant, to allow them to be safely transplanted.
Previously, you were contacted by our research team with information about the DEVELOP-UK study and have already signed an expression of interest form or a consent form, confirming your interest in taking part in the study.
As the study has progressed, the investigators leading the study in each of the 5 UK centres have met regularly to review progress and to learn from other experiences with EVLP around the world. This information is then shared with the independent Trial Oversight Committees.
Experience with the EVLP technique has been growing steadily around the world since the study began in April 2012. This includes experience using the specific EVLP machine that is being used in the DEVELOP-UK study. In particular, we were aware that an alternative way of using the machine, differing from our approach in only a few details, appeared to result in more donor lungs being available for transplant. In response to this, and with agreement from the Trial Oversight Committees, the investigators have made some changes to the way the EVLP technique is performed in the DEVELOP-UK study.
These changes mean that we are now using the machine in a way that in some other centres, results in a higher proportion of lungs being available for transplant as well as with good early results after transplant.
I have included with this letter an updated participant information sheet for your records. I encourage you to read this and if you have any questions please do not hesitate to contact us. In the first instance you can contact XXXX the DEVELOP-UK study research nurse at the hospital.
Your participation in the study remains entirely voluntary and I would remind you that before any transplant with EVLP improved lungs happens, you would be given the opportunity to reconfirm your willingness to receive them.
I would be very grateful if you could sign the attached acknowledgement form which confirms that you have received this updated information and return it to me in the prepaid envelope.
Yours sincerely

Signed

Principal Investigator

Appendix 10 End of study information sheet version 1.0, 22 October 2015

To be printed on the local trust headed paper

DEVELOP-UK
A Study of Donor Ex-vivo Lung Perfusion
in United Kingdom Lung Transplantation
ISRCTN: 44922411

End of Study Information Sheet

This information is being provided to you because you took part in the DEVELOP-UK research study while waiting for lung transplant. The study compared a new technique called Ex-Vivo Lung Perfusion (EVLP) with standard lung transplant. We asked the research question: is EVLP an effective way to increase the number of donor lungs available for lung transplantation in the UK? The study follow-up period has now ended, and this Information Sheet is to inform you of what happens now, and to explain how to access the study results, if you wish to do so.

You were informed when you gave consent what would happen to you when the study ended, via the Participant Information Sheet (PIS).

DEVELOP-UK is an observational study that followed what happened to participants during their first year after transplant. Therefore you will continue to receive standard medical care now the study has ended, as you did throughout your participation during the first year.

No samples of tissue or blood were collected from you that were not part of your standard medical care after transplant. However, when applicable the research team took small samples of lung tissue from donor lungs at the start and end of the EVLP process. These samples are currently being studied by the research team to help understand how EVLP works. Some of this work might be done in partnership with other research organisations or companies both inside and outside the UK. No identifiable personal information (from either donor or recipient) accompanies these samples.

The results of this study are currently being evaluated and will be published in widely read medical journals that review the quality of the results, and will be presented to doctors and scientists at national and international medical meetings. The results will also be reported to the Sponsor (The Newcastle upon Tyne Hospitals NHS Foundation Trust) and Funders (National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme, and Cystic Fibrosis Trust). The results will also be available on the study website once evaluation is complete: www.develop-uk.net; you can access this, if you so wish. As a trial participant you will not be identified personally in any publication, study report or presentation.

If you have any further questions, or would like to continue your involvement in clinical research, please contact the study team at your participating hospital.

Many thanks for your interest and participation in the study; you have made a vital contribution to research and the improvement of healthcare for patients waiting for lung transplantation in the future.

Appendix 11 Forms: extracts from case report form booklet

Date (dd/mm/yyyy)	☐☐ ☐☐ ☐☐☐☐
Hospital	
NHS BT Donor Number	

Criteria for standard transplant

Donation after Brain Death (DBD)

***Please record the correct answers to the following questions*:**

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

Donation after Circulatory Death (DCD)

***Please record the correct answers to the following questions*:**			
1	Satisfies criteria as for standard DBD donor lungs (if information available)	☐ Yes	☐ No
2	DCD Donors from Maastrict Category 2, 3 or 4	☐ Yes	☐ No
3	Systemic arterial PO2 > 40 kPa on 100% FiO_2 and 8 cm H_2O PEEP or equivalent FiO_2 : PaO_2 within 12 hours	☐ Yes	☐ No
4	Warm ischaemic time (WIT) < 30 minutes (WIT starts when donor systolic BP < 50 mmHg and / or O_2 sats < 70%)	☐ Yes	☐ No
5	Withdrawal of life support (WLS) time < 120 minutes	☐ Yes	☐ No
NOTE: If any of the above questions are answered "NO", the donor's lung is <u>not</u> eligible to be used for standard transplant.			

DEVELOP-UK Day of transplant

Date (dd/mm/yyyy)	☐☐ ☐☐ ☐☐☐☐
Hospital	
NHS BT Donor Number	

Criteria for EVLP Assessment and Reconditioning

Donation after Brain Death (DBD) or Donation after Circulatory Death (DCD) lungs

***Please record the correct answers to the following questions*:**			
1	Warm ischaemic time (WIT) > 30 minutes for DCD donors but < 60 minutes	☐ Yes	☐ No
2	Chest X-ray findings prohibitive to standard transplantation	☐ Yes	☐ No
3	Systemic arterial PO2 < 35-40 kPa and/ or selective PV gas < 30kPa on 100% FiO_2 and 8 cm H_2O PEEP	☐ Yes	☐ No
4	History of aspiration with bronchoscopic inflammation/soiling of the airway, or recurrent but not prohibitive secretions in the distal airway after adequate bronchial toilet	☐ Yes	☐ No
5	Difficult to recruit atelectasis	☐ Yes	☐ No
6	Sustained peak airway pressure > 30 cmH_2O	☐ Yes	☐ No
7	Unsatisfactory deflation test on disconnecting ET tube	☐ Yes	☐ No
8	Unsatisfactory palpation of the lungs identifying undetermined masses, nodules or gross oedema	☐ Yes	☐ No

9	Deterioration or cardiac arrest in the donor prior to retrieval such that uncertainty over assessment remains	☐ Yes	☐ No
10	Unsatisfactory inspection of the lung after administration of the preservation flush and procurement	☐ Yes	☐ No
11	Logistical reasons that will extend donor lung ischaemic time > 10-12 hrs and prevent donor organ use:		
	Viral studies awaited	☐ Yes	☐ No
	HLA compatibility studies	☐ Yes	☐ No
	Pathology assessment of indeterminate mass in any donor	☐ Yes	☐ No
	Awaiting recipient admission	☐ Yes	☐ No

NOTE: If any one or more questions are answered "YES", the donor's lung is eligible to be used for EVLP assessment and reconditioning

DEVELOP-UK Day of transplant

Date (dd/mm/yyyy)	☐☐ ☐☐ ☐☐☐☐
Recipient's Study ID	☐☐☐ ☐☐☐ ☐☐

Criteria for transplant after successful EVLP Assessment and Reconditioning

Donation after Brain Death (DBD) or Donation after Circulatory Death (DCD) lungs

***Please record the correct answers to the following questions*:**			
1	DBD and DCD donor lungs meeting criteria for standard transplant	☐ Yes	☐ No

2	Pulmonary artery pressure < or equal to 20 mmHg, whilst achieving stable perfusate flow of up to 70 ml/kg IBW/minute at 37°C	☐ Yes	☐ No	
3	Peak airway pressure <25 cms H2O while achieving adequate ventilation (tidal volumes up to a max 7 mls/kg IBW)	☐ Yes	☐ No	
4	Oxygenation capacity shown by delta PO_2 of >40kPa (perfusate LA PO_2 - perfusate PA PO_2)/FiO_2	☐ Yes	☐ No	
5	Selective PV gas > 30 kPa on 100% FiO_2 and 5 cm H_2O PEEP	☐ Yes	☐ No	
6	Stable or improving lung compliance and stable or falling lung resistance	☐ Yes	☐ No	
7	No pulmonary oedema build-up in the ET tube	☐ Yes	☐ No	
8	Satisfactory assessment on inspection and palpation	☐ Yes	☐ No	
9	Signed Consent to Continue Form by potential matched recipient to receive an EVLP reconditioned lung*	☐ Yes	☐ No	☐ N/A

NOTE: If any of the above questions are answered "NO", the donor's lung is <u>not</u> eligible to be used for transplant.

**** If Informed Consent Form was signed on the day of transplant the Consent to Continue Form is not required. Patients in standard transplant group are not required to re-confirm informed consent on the day of transplant if they have signed the Expression of Interest Form or the Informed Consent Form prior to the transplant.***

<u>Criteria for failed EVLP Assessment and Reconditioning</u>

Donation after Brain Death (DBD) or Donation after Circulatory Death (DCD) lungs

***Please record the correct answers to the following questions*:**

1	DBD and DCD donor lungs not meeting stated criteria for standard transplant	☐ Yes	☐ No
2	Not satisfying criteria for transplant after successful EVLP assessment and reconditioning	☐ Yes	☐ No

NOTE: If any of the above questions are answered "YES", the donor's lung is <u>not</u> eligible to be used for transplant.

Appendix 12 Patient and public involvement

Two lay member representatives were appointed to the Trial Steering Committee.

During the study, they attended:

- Trial Steering Committee meeting on 14 February 2012
- Trial Steering Committee teleconference on 8 October 2012
- Trial Steering Committee meeting on 16 April 2013
- Trial Steering Committee teleconference on 21 October 2013.

The lay member representatives contributed their personal patient experiences in advising the consent process and approaching patients, as well as designing patient-related study documents.

One lay member expressed concerns about running both the INSPIRE trial and DEVELOP-UK study at the same time, and asked what the Research Ethics Committee view might be. As a result, the Research Ethics Committee chairperson was contacted for further advice.

The lay representatives supported the restart of EVLP activity in the study and commented on the patient information sheet to provide additional information on how the lungs are handled. The proposed patient-related documents were subsequently approved by the Research Ethics Committee without any changes.

Appendix 13 Videos/podcasts

A video, entitled 'Reconditioned Lungs', with information about the study, has been posted on Transplant TV, an online channel for medical professionals, patients and carers to share scientific and medical information and stories about organ transplantation. Transplant TV is based at the Institute of Transplantation, Freeman Hospital, Newcastle upon Tyne (jointly between The NuTH NHS Foundation Trust and Newcastle University). The URL for the DEVELOP-UK video is: http://transplant.tv/portfolio/reconditioned-lungs/?id=272 (accessed 10 January 2016).

EME
HS&DR
HTA
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