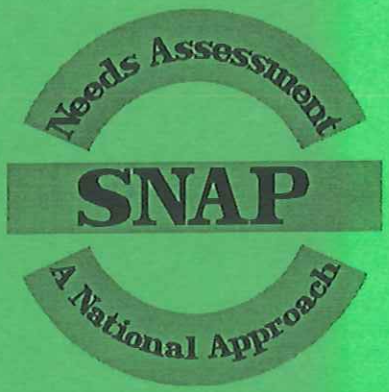
Scottish Needs Assessment Programme



Adult Heart-Lung and Lung Transplantation in Scotland

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Acute Services Network

Adult Heart-Lung and Lung Transplantation in Scotland

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Contents

EXECUTIVE SUMMARY

The accepted indication for heart-lung and lung transplants is, in general, end-stage lung disease. More than 90% of all transplants are performed for idiopathic pulmonary fibrosis, cystic fibrosis, bronchiectasis, emphysema, primary pulmonary hypertension or pulmonary hypertension secondary to congenital heart defect. Most transplant recipients are between the ages of 41 and 55 with very few over the age of 55.

In estimating likely future numbers it is the epidemiology of cystic fibrosis which provides the most accurate guide to demand as it is the most stable predictor of end stage lung disease suitable for transplantation. The various other indications for transplantation either occur more frequently in the older age groups, for whom transplantation is currently not recommended, or there are alternative non-surgical therapies available for an unpredictable proportion.

The average number of heart, heart-lung and lung transplants carried out in units in the USA, Australia and the UK each year is relatively low and there is wide variation from centre to centre. In 1994 in the UK the mean number of heart, heart-lung and lung transplantations carried out in each centre was 35, 9 and 16 respectively, considerably higher than the equivalent figures in the USA. The Scottish Cardiopulmonary Transplant Unit in Glasgow reported performing 32 heart transplants in 1995.

The epidemiological and activity data are poor or incomplete and we are unable to give a firm estimate of the number of Scottish residents who would benefit from a heart-lung or lung transplant. Our best estimate is a need for up to 20 heart-lung or lung transplants each year for Scottish residents. In 1994 there were 35 heart, 4 heart-lung and 15 lung cadaveric organ donations from Scotland. Scotland was a net exporter to other areas within the national transplant service of 18 heart, 4 heart-lung and 15 lung donations during the year.

Outcome and survival have steadily improved since the introduction of heart-lung and lung transplants in 1981. Currently in the UK the actuarial one-, three- and five-year survival following heart-lung transplantation is 62%, 46% and 38% respectively. For lung transplantation the one- and three-year survival rates are 61% and 42% respectively. Quality of life for those who survive the first three months after transplantation is generally good.

Although the unit in Glasgow has demonstrated good outcomes for heart transplantation, this is no guarantee of similarly favourable outcomes for heart-lung and lung. In particular the post-operative complications of heart-lung and lung transplants differ significantly from those of heart transplants. Units undertaking the former procedures need input from respiratory physicians with expertise in managing the unique complications of lung transplantation.

There is a dearth of economic analyses of heart-lung and lung transplantation. A key consideration following the establishment of any additional UK centres must be a comprehensive economic appraisal.

The ethical issues surrounding standard approaches to organ transplants have been well rehearsed and a clear consensus exists on most of these. However several issues have yet to be resolved. Transplant activity is being increasingly constrained by the shortage of suitable organs. A plateau in the number of solid organ donations has been apparent in the UK since 1990, whilst waiting lists continue to rise.

In the absence of a heart-lung or lung transplantation unit in Scotland, there are practical and social implications for potential Scottish recipients and their families. These include the considerable stress which travelling to centres in England puts on very ill patients from large parts of Scotland and the hardship and inconvenience which that arrangement creates for relatives. This is relevant not only during the assessment and perioperative periods but also during the prolonged period of specialist rehabilitation and follow-up.

RECOMMENDATIONS

1. The Scottish Office Department of Health should give approval in principle to the Scottish Cardiopulmonary Transplant Unit in Glasgow to commence heart-lung and lung transplantation.

2. National Services Division acting on behalf of the Scottish Office Department of Health should require the UKTSSA to provide separate epidemiological and activity data on Scottish residents and should monitor the comparative costs of transplants undertaken in UK centres.

3. National Services Division and the Scottish Cardiopulmonary Transplant Unit should jointly prepare a detailed service specification which would incorporate a requirement for up to 20 heart-lung or lung transplants each year.

4. The service specification should include the provision of input from respiratory physicians with expertise in managing the unique complications of lung transplantation.

5. The service specification should require a comprehensive economic appraisal to be undertaken following the introduction of the new service.

1 INTRODUCTION

Ministers decided in 1990 that Scotland should have a heart transplant facility. Bids were invited from Grampian, Greater Glasgow and Lothian Health Boards. On 16 December 1991, the Scottish Cardiopulmonary Transplant Unit opened at Glasgow Royal Infirmary and carried out its first heart transplant on 1 January 1992. The original decision was that the unit's programme should be restricted to heart transplantation until a secure base of experience had been established. Cardiopulmonary transplantation, it was envisaged, would be undertaken in the second or third year of the programme with single lung transplantation recognised as a further potential development. The unit projected that it would progress from 25 heart transplants a year in the beginning to a throughput of 50 heart transplants each year within three years. The unit has, until September 1995, completed 83 heart transplants since opening. The original target activity level has not been achieved and the decision to proceed to lung transplantation is under review.

The General Managers' Group and the Management Executive of the NHS in Scotland commissioned the authors to review current provision of heart-lung and lung transplantation in the UK and elsewhere and to make recommendations on the future provision of these services for the Scottish population.

This paper reviews the epidemiology of adult heart-lung and lung transplantation in the UK and overseas, adult being defined as a person over the age of 16, in order to assess the scope and need for transplantation for the population of Scotland. The paper also makes recommendations on the numbers of adult transplants needed and where these might be carried out.

2 EPIDEMIOLOGY OF HEART-LUNG AND LUNG TRANSPLANTATION

2.1 Historical perspective

The earliest attempts at human heart-lung and lung transplantation were undertaken in the 1960s. In subsequent attempts over the next two decades the high incidence of complications prevented the achievement of any long term clinical success. The development of an immunosuppressive regimen using a combination of cyclosporin and azathioprine led to the first successful long term survival of heart-lung and lung transplants in humans.

By 1990 the International Society for Heart Transplantation Registry had received data from 58 centres throughout the world on almost 1,000 cases, including 785 combined heart-lung, 157 single-lung, and 48 double-lung procedures.[1] At that time combined heart-lung and lung transplantation appeared to have reached a plateau at slightly less than 200 each year internationally as a result of limitations in donor availability. This scarcity of organs has contributed to the development of single lung transplantations as the most efficient use of available organs. In 1986 the concept of "domino" transplants was introduced, whereby the recipient receives a heart-lung transplant and donates his or her heart to a patient awaiting a heart transplant alone.[2]

Landmarks in the history of heart-lung and lung transplantation are shown in Table 1.[3]

Table 1
Landmarks in the history of heart-lung and lung transplantation

1946	Demikhov	Series of orthotopic and heterotopic heart-lung transplants without bypass or immuno-suppression
1968	Cooley	First human heart-lung transplants
1976	Borel	Cyclosporin A
1981	Stanford group	Long term success of heart-lung transplants
1985	Toronto group	Single lung transplants for pulmonary fibrosis
1986	Yacoub	Domino heart-lung transplants
1989	Cooper	Sequential single lung transplants for septic lung disease

2.2 Available techniques

There are four available types of procedure and these are outlined in Table 2 together with their advantages and disadvantages: [3]

Table 2
Types of procedure with advantages and disadvantages

Procedure	Advantage	Disadvantage
Heart-lung	longest established	uneconomical with donor organs (less so with domino)
	structurally normal heart	cardiac denervation
	maximal lung tissue	cardiac rejection
	coronary-bronchial collaterals for tracheal healing	transplant coronary atherosclerosis
		possibly more expensive
		possibly technically more difficult
En bloc double lung	maximal lung tissue	tracheal healing
	preserved cardiac innervation	
Single lung	maximal use of donor organs	limited lung tissue
	relative technical simplicity	bronchial anastomotic problems
		remaining disease in native lung
Sequential single lung	maximal lung tissue	bronchial healing
	preserved cardiac innervation	

Although the indications for the various procedures continue to evolve as more experience is gained with each, those for double-lung and combined heart-lung transplantations have remained fairly firm. Those for single-lung transplantation on the other hand have expanded rapidly to include conditions previously reserved for the other options. Table 3 summarises current thinking.[4]

Table 3
Current indications for different types of lung transplant

Heart-Lung	Single-Lung	Double-Lung
Primary pulmonary hypertension	Idiopathic pulmonary fibrosis	Cystic fibrosis
Secondary pulmonary hypertension	Emphysema	Emphysema
Cystic fibrosis	Primary pulmonary hypertension	Bronchiectasis
	Secondary pulmonary hypertension	Primary pulmonary hypertension

2.3 Indications and contra-indications for heart-lung and lung transplants

The accepted indication for heart-lung and lung transplants is, in general, end-stage lung disease.[5] More than 90% of all transplants are performed for idiopathic pulmonary fibrosis, cystic fibrosis, bronchiectasis, emphysema, primary pulmonary hypertension or pulmonary hypertension secondary to congenital heart defect.

Historically, only patients with a relatively good prognosis have been included in transplantation programmes. However, as experience and success have increased, the restrictions on patient entry have gradually been relaxed to the extent that there is now a body of opinion that no patient is too ill to be considered for the technically simpler single lung transplantation.

Theodore and Lewiston have argued that transplantation should be offered to "anyone with lung disease who is sick enough to need the operation, well enough to survive the waiting period of several months for a donor organ, fit enough to survive the surgery and courageous enough to deal with the complex post-operative care." Nevertheless, they believe that the upper age limit for heart-lung and lung transplant is 50 years and for single lung transplant 55 years, with no lower age limit. In their view only patients who have refrained from smoking for at least two years should be offered transplantation.[6] Others have proposed that psycho-social suitability and compliance need to be considered.[7] Scott, Dennis and Mullens have described end-stage lung disease clinically and physiologically,[8 9] and Egan has emphasised the need for a five year malignancy free interval.[10] It is worth noting that very different considerations apply in the case of paediatric transplantation.[11]

The major contraindications to transplantation are shown in Table 4.

Table 4
Major contraindications to transplantation

- Multi-organ failure such as liver, kidney or haematological
- Presence of an aspergilloma
- Most collagen vascular diseases or other autoimmune diseases
- HIV infection
- Active peptic ulcer disease
- Thrombo-emboli from abdominal and peripheral veins
- Musculo-skeletal disorders which limit ambulation
- Coronary artery disease (for single or double lung transplant)
- Previous pleurodesis or pleurectomy
- Presence of pan-resistant Pseudomonas cepacia infection which is refractory to a combination of antibiotics
- Serious psychological disorders
- Cerebrovascular disease
- Uncontrolled hypertension
- Irreversible coagulopathies
- Neuro-muscular disorders
- Systemic sepsis or any type of extra-pulmonary infection that cannot be adequately resolved
- Severe obesity
- Methicillin resistant Staphylococcus aureus (MRSA) infection

In a number of centres previous pleurectomy or pleurodesis are now considered only as relative contraindications. [7]

2.4 Demand for heart-lung and lung transplants

Cystic fibrosis is the most common single primary disease reported to United Kingdom Transplant Support Service Authority (UKTSSA) for heart-lung transplant recipients (22%), while for lung recipients fibrosing disease was the most commonly reported condition (20%) (Table 5).[12] The UKTSSA data do not discriminate between adults and children.

Table 5
Primary disease of heart-lung and lung transplant recipients in the UK and Republic of Ireland reported to the UKTSSA, 1 January 1985 - 31 December 1992

Recipient primary disease	Heart-lung transplant	Lung transplant	Total
Cystic fibrosis	127	24	151
Primary pulmonary hypertension	104	7	111
Fibrosing lung disease	16	55	71
Other heart-lung disease without pulmonary hypertension	37	33	70
Eisenmenger's syndrome	37	-	37
Congenital heart disease	35	-	35
Acute rejection	11	9	20
Other heart-lung disease with pulmonary hypertension	10	6	16
Other named conditions	10	5	15
Other unspecified conditions	42	92	134
Unknown	144	45	189
Total	**573**	**276**	**849**

In estimating likely future numbers it is the epidemiology of cystic fibrosis which provides the most accurate guide to demand as it is the most stable predictor of end stage lung disease suitable for transplantation. The various other indications for transplantation either occur more frequently in the older age groups, for whom transplantation is currently not recommended, or there are alternative non-surgical therapies available for an unpredictable proportion.

Cystic fibrosis is the most common lethal autosomal inherited disorder in the UK, with a prevalence of 1:2,000 live births. Approximately 400 babies are born in the UK each year with this condition - a chronic, progressive, obstructive disorder affecting the exocrine glands, in particular the lungs and the pancreas.[13] When the condition was first described in 1938, 80% of affected children died in infancy. Advances in medical care have now resulted in 80% of affected children surviving into adulthood with median survival for North American patients ranging from approximately 27 to 31

years. Nevertheless, 95% of patients eventually die of pulmonary insufficiency. [10] Apart from the physical effects of the disease, those affected suffer grossly impaired quality of life. Whilst isolation of the gene and the cystic fibrosis transport regulator protein (CFTR) have raised hopes for future genetic correction of the disorder, at present transplantation remains the only effective treatment for patients with the terminal cardio-pulmonary manifestations of the disease. [9]

Elborn, Shale and Britton have used cystic fibrosis population predictions and all cause mortality data to estimate the likely number of cardio-pulmonary deaths due to cystic fibrosis over the next decade and to estimate the number of such patients who are likely to benefit from heart-lung transplantation in England and Wales.[14] They concluded that there will be between 85 and 127 potential transplant recipients with cystic fibrosis each year over the next decade, nearly all of whom will be adults. However, between 1990 and 1992 fewer than 40 transplants were carried out each year for this condition.

As indications for heart-lung and lung transplants change with advancing knowledge, and as the threshold for treatment of conditions already considered appropriate for transplantation lowers, the principal determinant of future numbers of patients receiving transplants will be organ availability.

2.5 Heart-lung and lung transplant activity

The number of heart-lung and lung transplants performed in recent years in the UK has not kept pace with demand (Table 6) and the median time on the active waiting list for heart-lung transplant has increased from 424 days for patients registered in 1989-90 to 764 days for registration in 1991-92.[12, 15] Most transplant recipients are between the ages of 41 and 55.

Table 6
Activity levels and waiting list for heart-lung and lung transplants, UK, 1990 - 1994

		1990	1991	1992	1993	1994
Activity	heart-lung transplants	94	79	53	36	52
	lung transplants	52	72	90	95	116
	Total	146	151	143	131	168
Waiting list	for heart-lung transplant	219	219	236	190	186
	for lung transplants	69	111	145	151	193
	Total	288	330	381	341	379

2.6 Supply of organs for heart-lung and lung transplantation

It is clear that transplant activity is being increasingly constrained by the shortage of suitable organs. This phenomenon affects every country which has developed the ability to undertake this form of surgery [16,17,18] A plateau in the number of solid organ donations has been apparent in the UK since 1990, whilst waiting lists continue to rise.[19]

Overall there are three main causes of death resulting in cadaveric thoracic organ donation in the UK and Republic of Ireland. These comprise intracranial causes, road traffic accidents and other deaths from trauma. In the UK intracranial haemorrhage death rates have dropped by 70% between 1970 to 1990.[18] Deaths from road traffic accidents have also decreased dramatically in recent years due to improvements in road safety (Table 7).[20]

Table 7
Deaths from road traffic accidents in Scotland, all ages

Year	1990	1991	1992	1993	1994
Deaths	555	521	472	410	359

Approximately 84% of cadaveric solid organ donors die in intensive care units. In 1992 a national audit of deaths in intensive care in England and Wales concluded that brain stem death was a possible diagnosis in only 13.6% and a confirmed diagnosis in only 10% of the estimated 13,000 patients each year who die in these units.[21] Only half of the patients confirmed as brain stem dead eventually became donors with 30% of families refusing permission and 18% having a general medical contraindication to donation.

Moreover there are variations in the rate of organ donation retrieval across the UK and Republic of Ireland. [19] Scotland compares favourably with these other countries (Table 8).

Table 8
Cadaveric thoracic organ donations and retrieval rates (per million population) reported to UKTSSA by country

	1992		1993		1994	
Country	**organs donated**	**rate**	**organs donated**	**rate**	**organs donated**	**rate**
Scotland	66	13	43	8	54	11
England	343	7	382	8	441	9
Wales	21	10	17	8	22	10
Northern Ireland	25	16	9	6	14	9
Irish Republic	34	9	31	9	32	9

Amongst the general public awareness of the shortage of the supply of organs for transplantation is high. Surveys consistently show that about 70% of the population is in favour of donating organs after death. However, public opinion is almost equally divided over the issue of whether to change to a system of presumed consent for donation and is overwhelmingly against financial incentives for potential donors. [18]

A summary of the factors influencing the supply of donor organs is listed in Table 9.[18]

Table 9
General factors influencing the supply of donor organs

Death rates from relevant causes	road traffic accident death rates
	deaths from various forms of intracranial haemorrhage
Demographic and physical characteristics of a country	population density
	age structure
	ease of travel
Level of healthcare funding	number of intensive care units and transplant centres
Procurement arrangements	legal framework
	co-ordinating arrangements
Cultural factors	propensity for altruism
	religious and ethnic composition
	acceptance of brain stem death criteria
	support of the medical profession for transplantation

The relaxation of donor criteria which we have witnessed in recent years has not met the demand for organs. Even if there are changes in public attitudes towards making organs available and a change in legislation, human allograft transplantation may not meet the potential demand. Recent innovations in animal organ transplantation are being explored but are unlikely to become routinely available within the next decade.[22]

2.7 Matching donors and recipients

The selection of appropriate donors is also crucial to success,[23] and current recommended thoracic organ donor criteria are shown in Table 10.[3]

Table 10: Current recommended thoracic organ donor criteria

Age < 55 years
No history of malignant disease (except primary brain tumour)
No significant trauma
No lung aspiration or systemic sepsis
No previous cardiac or chest operation
Preferably non-smokers
No asthma
PaO_2 > 15 on F_iO_2 0.4 with a positive end expiratory pressure of 5 cm H_2O
Normal chest x-ray
No ulceration, erythema or deposits on mucus membrane on bronchoscopy
Methicillin Resistant Staphylococcus Aureus (MRSA) negative
Virology negative for Hepatitis B, Hepatitis C, and HIV

The pre-operative functional and nutritional status of the patient are important determinants of survival. [9, 24]A number of studies have confirmed the importance of matching donor and recipient for cytomegalovirus and emphasised the impact of technical aspects of the operation itself (Appendix 1) on survival.[25]

2.8 Outcomes and Survival

Outcome and survival have steadily improved since the introduction of heart-lung and lung transplants in 1981. Recent data from the USA, Australia and the UK are shown in Table 11.[12, 16, 17]

Table 11
Actuarial survival after heart-lung and lung transplants in the USA, Australia and UK

Percentage survival following transplantation		1 year %	3 year %	5 year %
USA	Single lung	70	51	-
	Double lung	67	51	-
	Heart-lung	59	48	-
Australia	Lung	61 - 78	-	-
	Heart-lung	70 - 75	-	-
UK	Lung	61	42	-
	Heart-lung	62	46	38

The relatively poor survival of heart-lung and lung transplant patients compared to other transplant recipients can be attributed to post-operative complications. In common with other transplants, mortality in the early period is related to immunosuppression, with infection the most common cause of death. [25] Other complications include acute rejection, renal failure, multi-organ failure, seizures, vocal cord palsy, transplant coronary disease, [3] and lymphoproliferative disorders. In addition, there is a unique complication of lung transplantation, the insidious development of severe obstructive lung disease known as bronchiolitis obliterans. [8, 26, 27, 28] Despite immuno-suppression 30% to 50% of lung transplant recipients will develop this condition within five years. Units contemplating all forms of lung transplantation require specialist input from respiratory physicians experienced in dealing with this condition.

Consensus has been reached on several aspects of clinical management, including the need for periodic pulmonary function tests to detect rejection, avoidance of use of prednisolone during the first 14 days after transplantation and annual left and right heart catheterisation with coronary arteriography. A number of unnecessary or undesirable procedures have also been identified, including electro-cardiogram and cyto-immunological monitoring as standard rejection monitoring techniques and routine steroid discontinuation after transplantation. [29]

2.9 Quality of life

Heart-lung and lung transplants are currently only offered to patients with end-stage disease, for whom the alternative is a steady decline until death. Researchers have stated, mostly intuitively, that the quality of life for those who survive the first three months after transplantation is generally good. [21, 24, 30, 31, 32] However, techniques have now been developed to measure overall well-being over time and these will help individual patients and families make difficult therapeutic choices and aid the formulation of health policy.[33]

The use of the Nottingham Health Profile three to six months after heart-lung and lung transplants in 31 patients demonstrated statistically significant differences in physical mobility, energy, sleep, social isolation and emotional reactions, and statistically significant improvements in areas of daily life covering home life, social life, sexual relationships, hobbies and holidays. [8] Another report on 81 patients who underwent single lung, double lung or heart-lung transplantation, although not quantified, found that social and professional re-integration can be achieved within a short time. [28]

2.10 Ethical considerations

The ethical issues surrounding standard approaches to organ transplants have been well rehearsed and a clear consensus exists on most of these. However, several issues have yet to be resolved. The first is the use of live healthy donors, the main ethical issues being that it may offend the fundamental medical ethic of *primum non nocere* (first do no harm), it may conflict with truly informed consent and runs the risk of encouraging a trade in organs. Shaw and colleagues have discussed the ethics of lung transplantation with live donors, principally family members.[34] The main benefit for the donor is psychological, the knowledge that one has saved the life of another. This has been found to be associated with an increase in

donor self esteem. The main risks include the risk of lobectomy to the donor, which in the short term has a mortality of under 1% but in the long term has unknown effects on pulmonary function, and the risk of undue pressure to donate from other family members.

The second issue concerns the ethics of moving to a system of presumed consent, "opting-out" of donation rather than "opting-in". The four ethical considerations here relate to respecting the wishes of the individual, the sensibilities of the relatives, trust in the medical profession and good medical practice. [18]

The third issue is the provision of financial incentives to families to make their deceased relatives' organs available for transplantation. In the United States Evans has argued that "in refusing to donate, families of the deceased have chosen to eschew altruism and in turn effectively pass on their grief to others".[35] Debate along these lines is some way off in the UK.

The fourth consideration is the use of organs from 'non-heart-beating cadaver donors', donors who have been declared dead by traditional cardio-pulmonary, rather than brain-orientated, criteria.[36] At present this consideration is only likely to be relevant to renal transplantation. The ethical issues are:

- How long must the heart have stopped beating before patients can justifiably be pronounced dead and their organs removed?
- Will manipulating the events surrounding death to accommodate organ procurement undermine a national consensus about the proper circumstances in which death may be hastened by treatment withdrawal or by giving pain medication?
- Will protocols compromise the care of some terminally ill patients?
- What safeguards could minimise the chance for abuse and maintain public trust?
- Will the institution of policies to obtain organs from such donors enhance or hinder public support and enthusiasm for organ donation?

The resolution of these ethical issues may in the longer term have a beneficial impact on organ availability. However, without major changes in national policy towards transplantation it is difficult to see how transplant activity can be significantly increased in the UK in the short term.

2.11 Transplant centre activity levels

There is a general consensus in the medical profession that there is a relationship between the frequency with which procedures are undertaken in specialist units and the clinical effectiveness of those units in relation to outcome. As a consequence of this, there is a tendency for low volume procedures to be concentrated in a small number of specialist units. This consensus has led Dennis and others to express the belief "that to ensure on-going success [heart-lung and lung transplants] should take place in a

limited number of centres where sufficient expertise has been acquired in all cardiac and pulmonary disciplines." [8]

There is, however, little in the literature on heart-lung and lung transplantation to support this contention, and there is now an emerging view that in relation to most other medical interventions evidence for this general principle is lacking.[37]

So how many procedures a year are required to ensure high clinical standards? There is no simple answer to this question. The average number of heart, heart-lung and lung transplants carried out in units in the USA, Australia and the UK each year is relatively low and there is wide variation from centre to centre as evidenced by the large standard deviations in relation to the means (Table 12).[16, 17, 19] The numbers of transplants carried out in UK centres are similar to the Australian experience but well above the equivalent figures for the USA. Any small increase in the number of UK centres would still result in the mean number of transplants in each centre being above those in the USA.

Table 12
Number of centres carrying out heart transplantation, heart-lung transplantation and lung transplantation, mean number of transplants during the year and standard deviation, by country, for the most recent annual data

Organ	Country	Year	Number of centres	Mean number of transplants	Standard deviation (SD)
Heart	Australia	1992	3	32	7.5
	USA	1993	145	16	13.5
	UK	1994	9	35	22.4
Heart-lung	Australia	1992	2	8	0.7
	USA	1993	29	2	1.5
	UK	1994	6	9	7.0
Lung	Australia	1992	2	14	9.2
	USA	1993	62	12	12.2
	UK	1994	7	16	17.1

2.12 Economic considerations

There is a dearth of economic analyses of heart-lung and lung transplantation.[38] Attempts have been made to cost components of the service, but these have not been set against potential benefits to the patient, the family or society. The only financial information available in the literature concerns either the cost of establishing,[39] and running a cardiopulmonary programme in Australia, [17] and the re-imbursement of costs through insurance schemes or unit costs in the USA. [6, 39, 40] Therefore, a key consideration following the establishment of any additional UK centres must be a comprehensive economic appraisal.

There are currently no published data on the cost of heart, heart-lung and lung transplants by individual UK centre. The available financial information relates only to the overall programme. However, purchasing arrangements for thoracic organ transplantation are currently under review by the Department of Health. The current estimated average unit costs of the UK thoracic organ transplant programme are shown in Table 13. The Department of Health advises that these costs should be interpreted with caution as there is considerable variation between centres, which are configured differently.

Table 13
Current average costs of the UK thoracic organ transplant programme 1995-6*

Procedure	Average cost
Assessment	£2273
Heart transplant	£21 282
Heart-lung transplant	£30 708
Lung transplant	£28 922
Annual follow-up	£3033

* Source: Department of Health

3 NEED, DEMAND, ACTIVITY AND ORGAN SUPPLY IN SCOTLAND

3.1 Need, demand and activity for heart-lung and lung transplantation in Scotland

The need for heart-lung and lung transplantation in Scotland may be greater than in other parts of the UK due to the high prevalence of respiratory disease in general. In addition, based on the estimated need in England and Wales, [14] each year it is expected that between eight and 13 adults with cystic fibrosis living in Scotland would benefit from heart-lung transplantation. There are three Cystic Fibrosis Centres in Scotland based at Gartnavel Hospital, Glasgow, Western General Hospital, Edinburgh, and one in Aberdeen and they had in mid-1995 79, 68 and 27 current adolescent and adult patients respectively.

Glasgow has referred 19 patients in the period 1992 -1995 for transplantation of whom 17 were suitable. Only two have had transplants, three are currently on standby on the active waiting list, six have been accepted and six have died on the waiting list.

Edinburgh has referred at least 14 patients in the period 1992-1995 for transplantation, all of whom were suitable. Only two have had transplants, three are currently on standby on the active waiting list, one has been accepted but is not on standby, one is undergoing assessment and seven have died on the waiting list.

Aberdeen has referred six patients in the past three years, of whom one is on standby on the active waiting list, one has been accepted but is not on standby, one was unsuitable and three have died on the waiting list.

The UKTSSA provides monthly updates of transplantation activity and the number of patients on the waiting list for organ transplantation by UK centre. It does not collect data by source of referral and is therefore unable to provide information on the number of Scottish residents who have been transplanted or are currently on the waiting list. For the purposes of this report, the National Services Division of the Common Services Agency approached each UK centre requesting this information. Harefield Hospital has not provided any information, despite repeated requests, but is known to have undertaken heart-lung transplants on at least two Scottish residents in 1994. Only two other centres, Newcastle and Papworth have transplanted Scottish residents in the last three years and the activity levels and current waiting lists are shown in Table 14.

Table 14 Activity and waiting list for heart-lung and lung transplantation for Scottish residents

Procedure	Centre	1992/3 -93/4	1994/5	Current waiting list
Heart-lung	Newcastle	4	1	1
	Papworth	0	1	2
Lung	Newcastle	14	3	15
	Papworth	1	0	0

Because the epidemiological and activity data are poor or incomplete we are unable to give a firm estimate of the number of Scottish residents who would benefit from a heart-lung or lung transplant. However, on the basis of the available information and of discussions with clinicians our best estimate is for a steady state need for up to 20 heart-lung or lung transplants each year. However, if the upper age limit for heart-lung and lung transplantation is raised above 55 years this will result in a major increase in need for this type of surgery. We have arrived at this estimate on the basis of the total number of adult transplants carried out on Scottish residents in 1994, seven, comprising the five listed above and another two of which we are aware from other sources. In addition, there are at least eighteen on the current waiting list. A number of the latter are likely to die before an organ becomes available. In addition, there is an indeterminate number who are eligible for transplantation but, for various reasons, are not currently referred for assessment. In short, there is at present a mismatch between activity and demand in Scotland.

Available data are not broken down by Scottish Health Board of residence. However, for the purposes of this paper, the lack of information is not critical, as, for the foreseeable future, any Scottish-based lung transplantation service is likely to be purchased and provided on an all-Scotland basis.

3.2 Supply of thoracic organs for donation in Scotland

In 1994 there were 35 heart, four heart-lung and 15 lung cadaveric organ donations from Scotland. The Scottish Cardiopulmonary Transplant Unit in Glasgow reported performing 17 heart transplants in 1994. Thus, Scotland was a net exporter to other areas within the national transplant service of 18 heart, four heart-lung and 15 lung donations during the year.

3.3 Other considerations

A key issue is the length of time which elapses between removal of the donor organs and their implantation in the recipient. Currently six to eight hours is considered to be the maximum time which can elapse to allow satisfactory gas exchange post-transplantation.[6, 23] A practical consequence of the time constraint is that some centres require potential lung recipients to live within two-and-a-half hours of the hospital to allow the minimal time needed to prepare the patient for transplantation once a suitable organ has been found.[6] In the absence of a heart-lung or lung transplantation unit in Scotland, there are practical and social implications for potential Scottish recipients and their families. These include the considerable stress which travelling to centres in England puts on very ill patients and the hardship and inconvenience which that arrangement creates for relatives. This is relevant not only during the assessment and perioperative periods but also during the prolonged period of specialist rehabilitation and follow-up. These considerations apply to people living in most areas of Scotland but we recognise that for a few travel time to an English centre is as easy as it is to Glasgow.

4 THE SCOTTISH CARDIOPULMONARY TRANSPLANT UNIT

4.1 Heart transplant throughput

The Scottish Cardiopulmonary Transplant Unit in Glasgow performed 95 heart transplants between 1 January 1992 and 31 December 1995, 24 in 1992, 22 in 1993, 17 in 1994 and 32 in 1995. Although it has not achieved the throughput of 50 cases each year originally anticipated,[41] the activity level in 1995 has increased. This throughput is similar to that of comparable units in the UK, Australia and the USA (Table 12).

4.2 Heart transplant survival

We have calculated actuarial survival rates for the Glasgow unit using the Kaplan-Meier method for transplants carried out between 1 January 1992 and 16 August 1995. These are shown in the figure below. Table 15 shows the survival rates at one, two and three years together with USA data for comparative purposes.[16] Similar data for Australia and other UK centres are not available. However, one-year survival for three Australian centres between 1988 and 1993 varied from 85.9% to 90.4%, and two year survival for two of these centres was 86%.[17] UKTSSA reports one-year survival after first heart transplantation between 1985 and 1992 as ranging from 66% to 81% in six UK centres which had followed up at least 50 transplants.[12] It should be noted that these survival rates have not been adjusted for case mix or the length of experience of the unit. We understand it is the usual practice for units to progress to more complex cases only after sufficient experience has been acquired. The favourable survival experience of patients receiving heart transplants in Glasgow should be interpreted in this light.

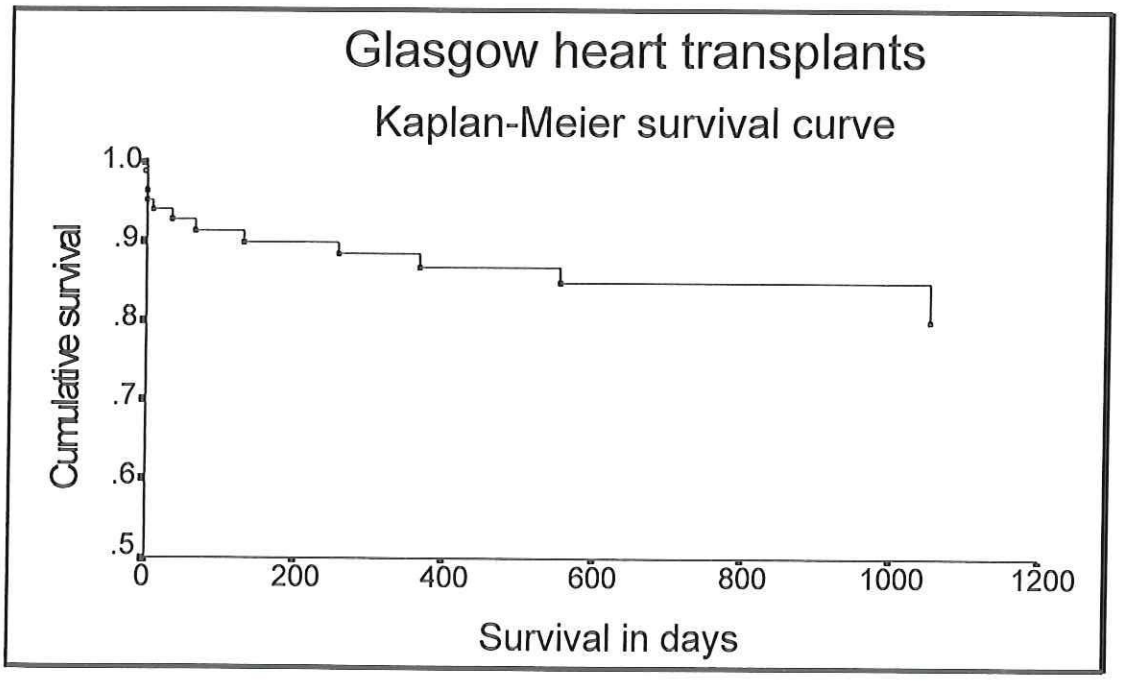

Table 15
Patient survival rates, using Kaplan-Meier method, for heart transplanted patients in the USA and Glasgow

		1 year survival		2 year survival		3 year survival	
	Period	**%**	**SE**	**%**	**SE**	**%**	**SE**
USA	1987-92	82.4	0.4	78.3	0.4	74.7	0.5
Glasgow	1992-95	88.4	3.7	84.7	4.3	79.8	6.3

4.3 Other considerations

Although the unit in Glasgow has demonstrated good outcomes for heart transplantation, this is no guarantee of similarly favourable outcomes for heart-lung and lung. In particular the post-operative complications of heart-lung and lung transplants differ significantly from those of heart transplants. As outlined earlier units undertaking these procedures need input from respiratory physicians with expertise in managing the unique complications of lung transplantation.

An additional heart-lung and lung transplant unit in Scotland may not increase overall UK transplant activity. However, a centre within Scotland may improve access for Scottish residents both because of physical proximity and as a result of the zoning arrangements introduced in November 1993. Under the latter the Scottish centre would have first refusal of all organs retrieved in Scotland. This may result in a marginal increase in the number of Scottish residents receiving transplants.

APPENDIX 1

CLINICAL DETAILS

1 Choice of procedure and recent developments

1.1 Heart-lung and lung transplantation

There remains considerable debate but, as yet, no clinical consensus over precisely when single or double heart-lung, lung or domino transplantation procedures should be undertaken. Until recently single lung transplantation was viewed as a rapidly developing procedure but many patients with end-stage pulmonary disease were considered not suitable for unilateral lung transplantation.[42] It was believed that in individuals with bilateral pulmonary sepsis such as cystic fibrosis, the remaining native lung would serve as a potential source of chronic infection in the immunosuppressed recipient after transplantation. There was also concern that in emphysema, unilateral transplantation might give rise to excessive inflation of the native lung with a shift of the mediastinum toward the transplanted lung.

1.2 Domino transplantation

The 'domino-donor' operation involves a substantial sub-set of patients with end-stage lung disease but with satisfactory cardiac function who serve as donors of cardiac allografts before undergoing heart-lung transplantation. A potential advantage of this procedure is that it avoids wasting a useable heart. On the other hand, some believe that en-bloc double-lung transplantation is superior because it excludes many of the complications caused by the cardiac portion of the transplant such as chronic and acute rejection as well as proliferative coronary vascular disease. It also eliminates the unnecessary removal of a heart from a patient who does not need cardiac replacement. Where en bloc double-lung transplantation is undertaken, the donor heart can still be used for transplantation to a cardiac recipient. [42]

The greatest experience of domino-donor procedures is at Papworth Hospital in Cambridge, where Oaks and colleagues found no difference in the three-month or one-year survival between domino and non-domino cardiac recipients. They also view the fact that many heart-lung recipients have elevated pulmonary artery pressure and a 'conditioned' hypertrophied right ventricle as a theoretical advantage in cardiac recipient patients with elevated pulmonary vascular resistance.[43] Overall, however, their view is that the issues associated with the allocation of heart-lung blocs are not settled and await long-term follow-up of sequential double-lung and single-lung recipients. Starnes et al believe that the debate will probably be resolved in favour of double-lung transplantation because of the shortage of heart-lung blocs and lack of scientific support for one operation over the other.[44]

1.3 Segmental transplants

Single segmental lung transplants have been carried out on a small scale since 1990 in the United States involving living donors, usually parents or siblings, who have donated lobes of one of their lungs to their relatives. [16]

The ethics of this are unclear, and have been the subject of considerable debate. [34]

1.4 Single lung transplants

Bhatnagar has summarised why single-lung transplantation is now a more attractive option than double-lung transplantation.[45] First, as the lung transplantation procedures increase in number the donor pool becomes smaller. Single-lung transplantation doubles the donor organ utilisation and halves the waiting time before transplantation. Second, in patients with emphysema, because of their large thoracic cavity, single-lung transplantation is technically a straightforward procedure. Third, there is less frequent need for cardio-pulmonary bypass in single lung transplantation. Fourth, due to simplicity, single lung transplantation is a more attractive option in a much older patient population suffering from emphysema. Nevertheless, the consensus remains that both lungs must be replaced if significant infection is present, for example in individuals with cystic fibrosis or bronchiectasis. [5, 24]

1.5 Age and sex of transplant recipients

The mean age for heart-lung and lung transplantation is presently 30 years; single and double lung transplant patients on average being slightly older (mean ages 45 and 42 years, respectively). In contrast to the marked male predominance in heart transplantation, 57% of heart-lung transplant recipients have been female, although males account for 62% of single and 67% of double lung transplant procedures.

2 Technique

2.1 Heart Lung Transplantation

After mediastinotomy and institution of cardio-pulmonary by-pass, the heart and each lung are excised separately, care being taken not to injure the phrenic or vagal nerves. The trachea is transected approximately two centimetres above the carina. For implantation, the left lung is gently pushed through the ipsilateral pericardial incision into the left chest cavity; the right lung is manipulated below the remnants of the right atrium into the right chest. The organs are implanted by anastomosing in turn tracheae, right atria, and ascending aorta.[46] Meticulous attention to posterior mediastinal haemostasis must be observed. [7]

2.2 Lung Transplantation

Single lung transplants are performed through a postero-lateral thoracotomy. Patients are intubated with a double-lumen endotracheal tube to allow the lung being replaced to be deflated. This allows the hilar structures to be mobilised and divided. All patients with pulmonary hypertension require the institution of cardio-pulmonary by-pass. The diseased recipient lung is then removed and the bronchial anastomosis accomplished. The pulmonary artery anastomosis is then completed, as is the anastomosis between donor and recipient left atrial cuffs. The lung is flushed antegrade and retrograde with blood, and the clamps are released,

restoring perfusion to the lung. When haemostasis at the pulmonary hilum is secure, ventilation of the graft can be initiated. [7]

2.3 Double Lung Transplantation

The chest is entered through a midline incision of the chest, a median sternotomy. Because complete cardiopulmonary bypass is unnecessary, a right atrial cannula is all that is required and is placed through the right atrial appendage. The recipient pulmonary artery is divided, the superior and inferior pulmonary veins are divided and finally the bronchus is divided. The double lung block is divided into its constituent right and left lungs, and the appropriate lung is placed in the thorax. The airway anastomosis is then performed, and the pulmonary veins are attached to the left atrium and the pulmonary artery anastomosis is performed last.

3 Complications

Post operative complications of heart-lung and lung transplantation include acute rejection, infection, renal failure, multi-organ failure, seizures, vocal cord palsy, transplant coronary disease in heart-lung transplantation, [3] lymphoproliferative disorders and bronchiolitis obliterans. [26] In addition there are complications related to problems with the bronchial anastomosis, including dehiscence, mucosal necrosis, infection, haemorrhage, and late bronchostenosis. Ischaemia of the donor bronchus subsequent to division of the bronchial arterial supply, the rejection response that takes place at the anastomotic site, and the toxic effects of immunosuppressive drugs to prevent allograft rejection may all play a role in the pathogenesis of these complications.

3.1 Acute rejection and bronchiolitis obliterans

Acute rejection can occur in a transplanted lung, with widespread lymphocytic infiltration of the perivascular area of the lung bed, and produce respiratory failure in a matter of hours.[47] If the condition is detected in its early phases, it can be reversed. After six months acute rejection is uncommon. The lung is then vulnerable to another condition - the insidious development of severe obstructive lung disease in a matter of weeks - bronchiolitis obliterans. [6] Obstructed lymph drainage, irreversible denervation, infections and in particular continuing rejection episodes may be responsible aetiologic factors.[46] If, despite treatment, the disease of bronchiolitis is far advanced, retransplantation of the heart and lungs remains the only therapeutic choice. Despite immunosuppression, 30 - 50% of lung allograft recipients will subsequently develop obliterative bronchiolitis by five years. The onset of obliterative bronchiolitis has a major psychological impact on patients which requires a compassionate and tender handling.[48] Obliterative bronchiolitis is now the major obstacle for continuing survival and a morbidity-free life, and since its first description in 1984 has been a continuous challenge for lung transplant teams world-wide.[49]

3.2 Coronary disease in heart-lung transplantation

In heart-lung and lung transplantation, chronic cardiac allograft rejection takes the form of coronary artery disease, and the presence of obliterative

bronchiolitis is a significant risk factor for coronary artery disease in long-term heart-lung transplant recipients.[50]

3.3 Effects of immunosuppression

Mortality in the early period is related to immunosuppression, with infection the most common cause of death. [25] The more common problematic infections include Pseudomonas aeruginosa, cytomegalovirus (CMV), herpes simplex virus, Pneumocystis carinii and Aspergillus fumigatus. [9] Ciulli et al also describe infection with Klebsiella, streptococcus, haemophilus, candida and enterococci.[51] In addition, there are consequences of being a transplant patient related primarily to the requisite immunosuppression, other than infection. There is heightened risk of a variety of neoplastic disorders, including lymphoproliferative disorders, the most common type of neoplastic disorder associated with transplantation. Development of a transplant lymphoma is thought to occur in approximately 5% of recipients, although this is not unique to lung transplant recipients. Recently is has been suggested that some B-cell lymphomas observed in the lung may be a histological manifestation of response to viral infection, inasmuch as resolution of the pulmonary process has been observed after therapy with high-dose Acyclovir.[10]

4 Lung preservation for transplantation

There is a clear correlation between the manner in which donor organs, particularly lung (which is especially vulnerable to deterioration), are dealt with and the success of the transplant procedure.[52] A key issue is the length of time which elapses between removal of the donor organs and their implantation in the recipient. Currently six to eight hours is considered to be the maximum time which can elapse to allow satisfactory gas exchange post-transplantation. [6, 23] Techniques for preserving donor lungs, listed by the UKTSSA include:

- donor core cooling (Harefield Hospital)
- colloid pulmonary artery flush (Papworth Hospital)
- crystalloid pulmonary artery flush plus additives (Rest of World) e.g. Euro-Collins solution

The over-riding problem in lung transplantation is shortage of donor organs. If the safe ischaemia time could be extended to 12 hours there would be a bigger pool of donors, better opportunities for prospective tissue-typing and much more time to organise the recipient operation. [31] There is progress in the field of organ preservation[53] but there is clearly a limit to the practical length of ischaemia time which can be achieved. It is likely that for the foreseeable future increasing the availability of transplantation without excessive social disruption to the affected families will require further decentralisation of the transplantation programme.

APPENDIX 2

GLOSSARY

Orthotopic - this term is used to describe operations where an organ is transplanted to a recipient in a position other than its normal anatomical site.

Heterotopic - this term is used to describe operations where an organ is transplanted to a recipient in its normal anatomical site.

Allograft - graft of an organ or tissue to a recipient of the same species.

Eisenmenger's syndrome - this term is used to describe the onset of high blood pressure in the lungs, (pulmonary hypertension), secondary to a specific congenital heart condition, namely ventricular septal defect. The abnormal connection between the left and right ventricles of the heart results in increased blood flow to the lungs, a process known as left to right shunting. In time this gives rise to increased resistance in the pulmonary arterial circulation and pulmonary hypertension. The development of pulmonary hypertension significantly worsens the prognosis.

Kaplan-Meier survival curve - this is a method of presenting a life table which takes into account incomplete follow-up of patients.

Sequential single lung transplant - this is the most commonly used type of double lung transplant technique. The two donor lungs are transplanted separately from an individual in sequence into a single recipient. This technique eliminates the need for bypass.

APPENDIX 3

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